# American Heart Journal

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## Obituary

### Gustav Nylin

**1892-1961**

*By Gunnar Biörck, Stockholm, Sweden*

Professor Gustav Nylin, of Stockholm, died August 6, 1961, from cardiac infarction. He was born in 1892. Next of kin are his wife Ingrid, two daughters, and grandchildren.

With the passing away of Gustav Nylin, Swedish medicine has lost one of its internationally most prominent personages.

What Gustav Nylin achieved as a physician depended largely on his genuine appreciation of scientific research. His career was unusual: as a practitioner and school physician he became interested in the physical development of school children, and he presented his thorough observations in this field in the form of a doctor's dissertation. This important work opened the doors of the Iacobaeus Department of Medicine at the Serafimer Hospital, where he had the opportunity to put into practice and further develop his views on the problems of the physiology of the heart and circulation.

Contrary to more old-fashioned conceptions, hampered overmuch by pathological-anatomical ideologies, Gustav Nylin considered it essential to study scientifically heart function in living man with the aids of modern medicine. At an early stage he devised a test for heart function, and together with Liljestrand and Lysholm developed a method for a quantitative study of the heart roentgenologically. This work awakened his subsequent interest in blood-volume conditions in different diseases of the circulation. The


Professor Gustav Nylin, 1892-1961.

medical use of radioactive isotopes opened up an entirely new approach to these problems—and in cooperation with de Hevesy he became a pioneer within a field of research which later became universal.

During his last years, the circulation of the brain especially caught his interest, and to the very last, aided by American funds, Gustav Nylin worked actively in this field of research in the laboratory which the city of Stockholm placed at his disposal when he retired from his position as head physician at the South Hospital in Stockholm.

Gustav Nylin gave only a short period of his life to the Serafimer Hospital. He subsequently became head physician at Sabbatsberg's Hospital, and thereafter at the cardiac department of the South Hospital. He had a burning passion for research and conveyed this attitude also to his co-workers. As the years went by, more and more foreign physicians and research workers visited his department.

Because of his undaunted activity and devotion to cardiology, Gustav Nylin played a prominent part as an organizer both at home and internationally. He became the first chairman of the Swedish Cardiological Society, and also presided over the Second European Congress in Stockholm, 1956, as chairman of the European Cardiological Society. He was a member of several scientific societies abroad and was often asked to lecture the world over.

Gustav Nylin was an enthusiastic person and a faithful friend who was always ready to help his fellows and his patients. Despite success he remained simple and unassuming in his ways.

Swedish cardiology of today is to a great extent based on the work of Gustav Nylin and on the impulses he has given. He will be sadly missed by many cardiologists all over the world who are indebted to him for all the knowledge, encouragement, and support he has given.

# Editorials

## Concentrating mechanism of the kidney from a comparative viewpoint

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The mechanism for making a urine that is osmotically more concentrated than the blood is found in three groups of animals only: the insects, the birds, and the mammals. This, one might say, is reasonable. All three groups are terrestrial, and consequently the conservation of water is essential. In an early stage of evolution the ability to make a urine that was more concentrated than the blood must have become part of the adaptation to a terrestrial habitat.

This, however, is an oversimplification. There are other groups of animals which are also terrestrial, but which do not possess kidneys that can produce a concentrated urine. Furthermore, a marine animal, like the fish, is also faced with a need for the conservation of water and the excretion of salt, and yet its kidneys are only capable of producing a urine that is almost isotonic with the blood but never hypertonic.

Thus, the ability to concentrate the urine was not an essential feature of water conservation but came about as a rather special adaptation. In the insects the mechanism through which a concentrated urine is formed is radically different from that of birds and mammals. The insect kidney, the Malpighian tubules, also have an origin different from that of all other kidneys in the animal kingdom. The Malpighian tubules start as an outgrowth from the intestine and probably originate from the endoderm. In all other animals, invertebrates as well as vertebrates, the kidney is derived either from the ectoderm, ectoderm and mesoderm, or mesoderm alone.

In the following, I will attempt to show that all kidneys (except the insect kidney) basically operate in a similar manner in handling salt and water along the tubule, but that the bird and, to a greater degree, the mammalian kidney through ingenious engineering can produce a urine that is more concentrated than the blood.

Let us begin with a quite primitive kidney, the nephridium of an earthworm (Fig. 1,*A*). An earthworm living in a moist environment is essentially a fresh-water animal. The osmotic concentration of the body fluids of the earthworm is about two thirds of that of mammals. Water is taken up by osmosis, and consequently there is a need for the excretion of water with conservation of salt, i.e., the excretion of a urine that is highly hyposmotic to the blood.

The functional parts of the nephridium are roughly similar to those of the mammalian renal tubule: a nephridiostome corresponding to the glomerulus, a proximal and a distal tubule. Ramsay[1] performed micropunctures on the nephridium and found that in the proximal tubule the osmolality of the tubular fluid remains identical with that of the coelomic fluid,

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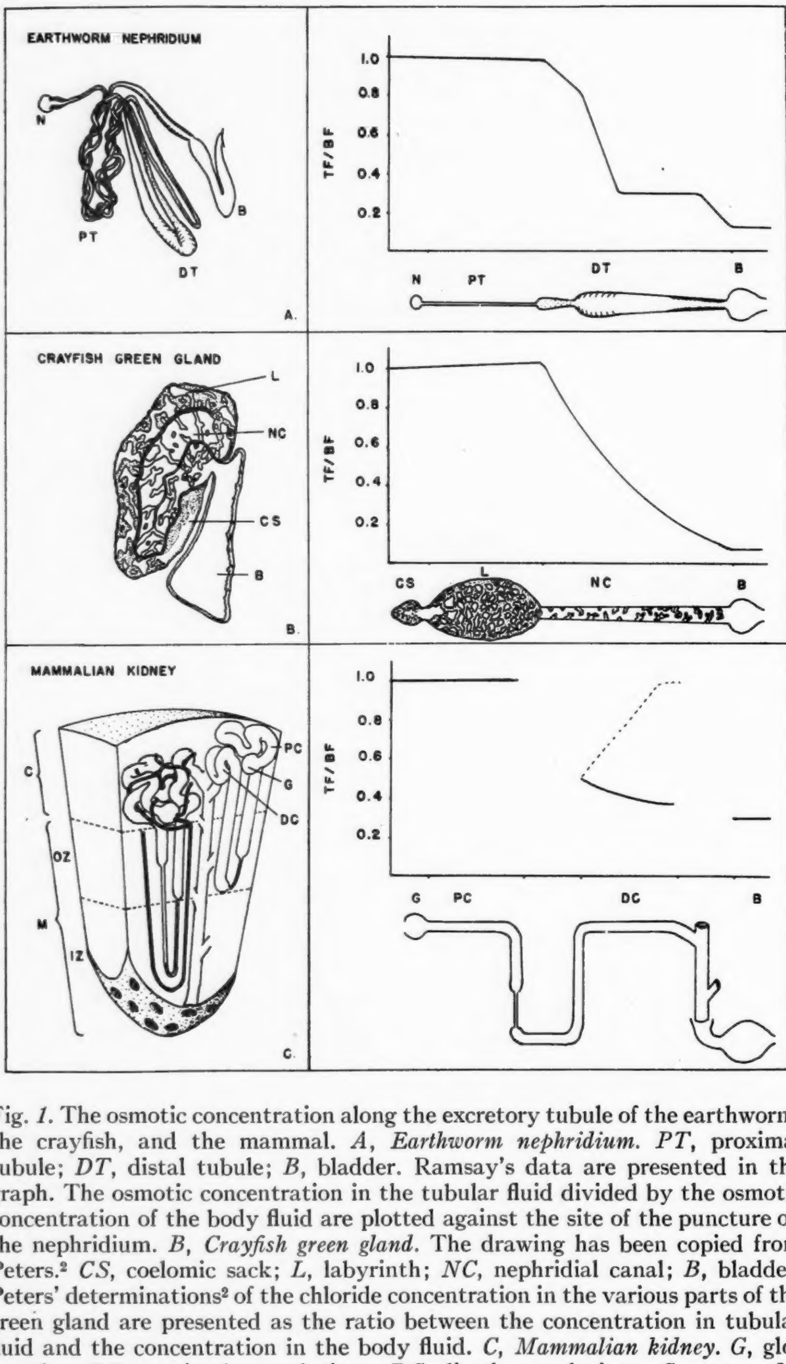


Fig. *1.* The osmotic concentration along the excretory tubule of the earthworm, the crayfish, and the mammal. *A*, *Earthworm nephridium. PT*, proximal tubule; *DT*, distal tubule; *B*, bladder. Ramsay's data are presented in the graph. The osmotic concentration in the tubular fluid divided by the osmotic concentration of the body fluid are plotted against the site of the puncture on the nephridium. *B*, *Crayfish green gland.* The drawing has been copied from Peters.[2] *CS*, coelomic sack; *L*, labyrinth; *NC*, nephridial canal; *B*, bladder. Peters' determinations[2] of the chloride concentration in the various parts of the green gland are presented as the ratio between the concentration in tubular fluid and the concentration in the body fluid. *C*, *Mammalian kidney. G*, glomerulus; *PC*, proximal convolutions; *DC*, distal convolutions; *C*, cortex; *M*, medulla; *OZ*, outer zone of the medulla; *IZ*, inner zone of the medulla. Along the ordinate are given the osmotic concentrations in the tubular fluid divided by the concentration in the blood. The solid line represents the data obtained by Wirz[4] from rats producing a hypotonic urine. The dotted line represents data obtained in rats during low diuresis when the urine was hypertonic (Wirz[4] and Gottschalk and Mylle[5]).

whereas in the distal tubule the osmolality drops sharply (Fig. 1,*A*).

A similar finding has been reported by Peters[2] in another fresh-water animal, the crayfish. The crayfish kidney, the green gland, is situated in the head of the animal, and the bladders open to the outside through the operculae near the antennae (Fig. 1,*B*). In the coelomic sack, that functionally corresponds to the glomerulus

in a mammal, and in the labyrinth that corresponds to the proximal tubule, the concentration of chloride remains the same as in the blood, but in the nephridial canal the concentration of chloride decreases and the urine becomes hypotonic.

In all other invertebrates and vertebrates the mechanism for formation of a hypotonic urine appears to be the same. Either fluid from the coelomic cavity or a filtrate from the blood moves through the proximal and distal tubules. In the proximal tubule it remains isotonic to the blood, but in the distal tubule it becomes hypotonic through reabsorption of salt. In many marine animals the ability to dilute the urine is missing, and in these animals it is found that the distal tubule is missing. This is true in fish as well as in crustaceans or annelids.

In the kidney of bird and mammal, both proximal and distal tubules are present, and these animals can also make a dilute urine. Even the kangaroo rat, which never drinks water in its wild habitat and normally produces a tremendously concentrated urine (about 6 or 7 Osm) makes a highly dilute urine when given diluted milk as the only source of food.

Micropunctures on rat and guinea pig kidneys were first performed by Walker and associates[3] from the cortical surface, where the proximal and distal convoluted tubules of short looped nephrons are accessible (Fig. 1,*C*). Through these studies and through other studies by Wirz[4] and by Gottschalk and Mylle[5] it was shown that whereas the fluid along the proximal convolutions remains isosmotic to the blood, the fluid in the early distal convolutions is distinctly hyposmotic.

Wirz showed that when the rat is in water diuresis, the fluid in the distal convolutions remains hyposmotic. When the animal is producing a concentrated urine, the fluid is still highly hyposmotic in the early distal convolutions, but becomes isosmotic to the blood as it proceeds toward the distal end of the distal convolutions. These later findings were beautifully confirmed by Gottschalk and Mylle.[5] The results are similar to the findings in the earthworm and the crayfish, in that the osmotic concentration remains identical to that of the blood in the proximal tubule but becomes lower in the distal tubule. Thus, also in mammals, the function of the distal tubule is distinct from that of the proximal tubule, in that the tonicity of the fluid inside the tubule is lowered through the active reabsorption of salt by the tubular wall. In the proximal tubule, too, there is active reabsorption of $Na^+$, but in the proximal tubule the permeability to water is so great that no difference in tonicity can be detected with available methods.

The ultrastructures of the tubular cells that are capable of creating a difference in tonicity are remarkably alike. Electron micrographs of a cell from the distal tubule of a mouse[6] and from the nephridial canal of a crayfish[7] show deep basal infoldings with mitochondria lined up between the infoldings. These cells also resemble those of the ducts of salivary glands and sweat glands, for which the same function, namely, the active reabsorption of salt, has been shown.

The next question must be: "Since the renal tubules are functionally alike, why can the crayfish and the earthworm make a hypotonic or isotonic urine only, whereas a mammal can make a urine that is several times as concentrated as the blood?"

The answer is found in another part of the renal structure, the loop of Henle. The only animals that possess the loop are the birds and the mammals. In the lower vertebrates (fish, amphibians, reptiles) the renal tubules are convoluted throughout their length. In the birds, most of the nephrons are of the reptilian type, but in addition there are some with a loop of Henle. In the mammals, all the nephrons have a loop, some short and some long. It is an important feature that the loops are parallel with each other and parallel with the collecting ducts and with the capillaries (see Fig. 1,*C*).

The function of Henle's loop has been very poorly understood until quite recently. It was suggested by Peter[8] (1909) that the length of the thin segment is related to the maximal concentration ability, and that active reabsorption of water takes place in the thin segment. This notion, however, was discarded, partly on a histologic basis. The cells in the walls of the limbs simply did not look as though they were able to do osmotic work. H. W. Smith[9] (1950) sug-

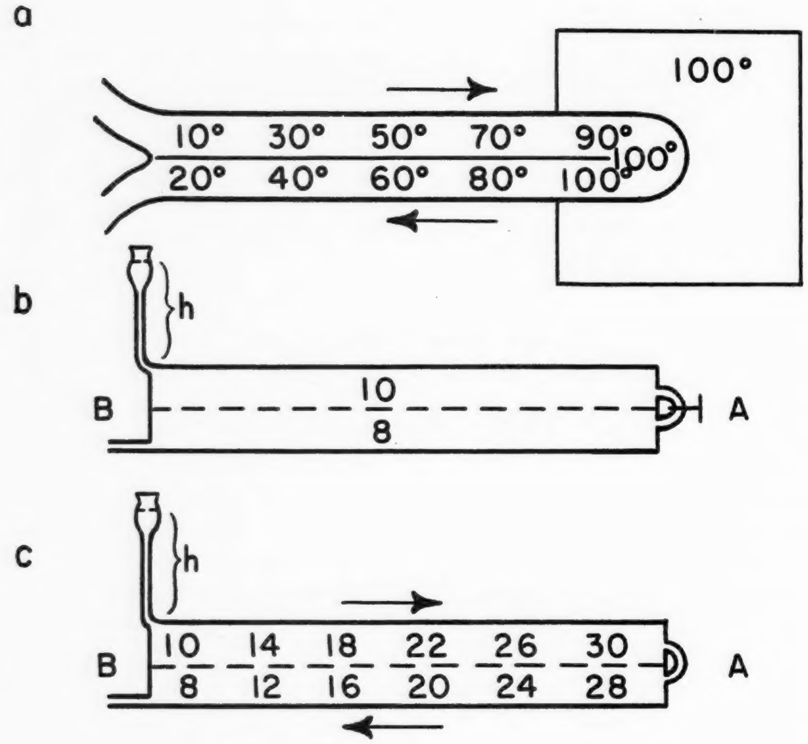


Fig. 2. *a*, A countercurrent exchange system. A pipe with water enters an oven with the temperature of 100°C. The incoming water is heated by the outgoing water, and the heat in the oven is conserved. *b*, A diagram modified from Hargitay and Kuhn.[10] The system is filled with a salt solution. The valve at *A* is closed. Due to the difference in hydrostatic pressure between the upper and lower part of the tube, the water diffuses across the semipermeable membrane and the solution in the lower part becomes dilute compared to that in the upper part. *c*, A countercurrent multiplier system as suggested by Hargitay and Kuhn.[10] In this system the force which creates the osmotic gradient is the hydrostatic pressure difference between the two tubes. (In the kidney the force is not a hydrostatic pressure difference but the sodium pump.) If the valve at *A* is open and a steady flow of solution is maintained in the direction indicated by the arrows, a concentration gradient in the tubes will be established.

gested that the urine becomes isotonic with the blood in the thin limb. In 1951, however, a paper was published by Hargitay and Kuhn[10] which has caused something of a revolution in renal physiology—"Das Multiplikationsprinzip als Grundlage der Harnkonzentrierung in der Niere." However, another 5 to 7 years elapsed before these new thoughts became accepted in this country.

The first experimental verifications for this theory were supplied by Wirz, Hargitay and Kuhn[11] and by Wirz[12]: It was shown that the osmotic concentration of the renal tissue rises from cortex through outer and inner zones of the papilla. Samples of blood from the vasa recta at the tip of the papilla were found to have the same osmotic concentration as the simultaneously formed urine. Later, Gottschalk and Mylle[5] showed that, also, the fluid inside the loop of Henle at the tip of the papilla is isosmotic with the urine.

Hargitay and Kuhn[10] proposed that the loop of Henle functions as a countercurrent multiplier system. Before going into greater detail it is necessary to explain how a countercurrent exchange and a multiplier system operate: Water in a straight pipe is sent through an oven; the temperature of the oven is 100°C., and that of the water in the pipe is 10°C. During the passage through the oven the water attains the same temperature as that of the oven. If 1 liter of water passes through the pipe per minute, then approximately 90 kilo-

calories are removed from the oven per minute. If we designed the system as a countercurrent exchange system, however, we could send the same amount of water through the oven per unit time, but carry only a very small amount of heat out of the oven. This could be done if we bent the pipe so that the incoming stream of water was in close contact with the outgoing stream. Now, the outgoing water would give off heat to the incoming stream, and by the time that the water left the system it would be only slightly warmer than that coming in (as shown in Fig. 2,*a*). The heat in the oven would be conserved and a temperature gradient along the loop would be established. This is a typical passive countercurrent exchange system. It could apply equally well to a system in which a dilute salt solution was carried through a tube with semipermeable walls into a reservoir containing a more concentrated solution. In this case, water would move across from the incoming to the outgoing stream, and a concentration gradient along the loop would establish itself. There are several biologic examples of countercurrent exchange systems. In the flippers of seals and whales the arterial and venous blood vessels are in close contact with one another, so that the heat from the arterial blood going to the flipper is given off to the cold venous blood which is returning. In this way the blood is cooled before it reaches the flipper, and loss of heat to the surrounding water is minimized.

In the swim bladder of fish, a very beautiful example of a countercurrent exchange system is found in the rete mirabile, the blood supply to the gas gland. (The rete mirabile probably also functions as a countercurrent multiplier system, but this aspect of its function will be disregarded here.) In the rete the incoming arterioles split up into numerous capillaries, which are completely interspersed between the outgoing venous capillaries. The arrangement is so perfect that each arterial capillary is surrounded on all sides by venous capillaries, and vice versa.[13] The functional significance of this arrangement is that oxygen can diffuse readily from venous to arterial capillaries, and, thus, the high oxygen pressure in the swim bladder is preserved.

In the mammalian kidney the vasa recta are arranged in capillary bundles. A recent study[14] of these bundles has revealed that the structure resembles very closely the rete mirabile of the swim bladder, with the same complete interspersion between venous and arterial capillaries. From what is known at the moment, the capillaries function as a passive countercurrent exchange system in the kidney. In other words, they can maintain a difference in concentration but they cannot create it.

A countercurrent system in which a difference in concentration is created is a *multiplier system*. In such a system a force is needed and energy must be expended. Hargitay and Kuhn, in their original model, proposed that the force that caused concentration of the glomerular filtrate in the loop of Henle was the hydrostatic pressure. This has since been shown not to be the case, but I will use their model to show how a multiplier system can operate. The system is shown in Fig. 2. Both the upper and lower tubes are filled with the same salt solution. The membrane which separates the two solutions is permeable to water but not to salt. First, we close the valve at *A*. The higher hydrostatic pressure in the upper tube will cause the water to move across the membrane to the lower tube. The solution in the upper tube will become more concentrated, and the solution in the lower tube, more dilute. A steady state will be reached when the osmotic pressure difference balances the hydrostatic pressure difference (Fig. 2,*b*). Now, if we open the valve, some of the more concentrated solution will flow into the lower tube. Again water will diffuse across. The solution on top will become still more concentrated. The process can be repeated, and each time the concentration near the loop will increase. If a steady slow flow is maintained, the result will be that the concentration at the tip of the loop will be several times higher than the concentration at the inflow and outflow sides (Fig. 2,*c*). This is a true countercurrent multiplier system, and the force is the hydrostatic pressure.

In the kidney the force *is not* the hydrostatic pressure. There is now convincing evidence that the active transport of sodium out of the ascending limb of the loop

of Henle is primarily responsible for the osmotic concentration gradient created by the loop of Henle. When a mammalian kidney is analyzed for a number of solutes, it is found that the two substances that contribute to the greatest degree to the osmotic gradient found along the loop of Henle are sodium (with its accompanying anions) and urea. The part that sodium contributes is independent of the amount of sodium that appears in the urine.

When micro samples are taken out of the proximal and distal convolutions, it is found that although the concentration of sodium in the proximal tubule under most circumstances is almost identical to that of the blood, it is considerably lower in the early distal convolutions. It can be calculated that during the passage through the short loops of Henle about one half of the water that enters and about three fourths to four fifths of the sodium that enters leave the tubule.[15] Urea, on the other hand, enters the tubule in the loop of Henle in relatively large amounts, i.e., at the end of the proximal tubule only one third of the filtered urea is left, but in the distal convolutions, more urea is present than the total amount filtered. Where this urea comes from is not quite clear at the moment. It may be secreted or it may diffuse into the tubule.

The sodium that is actively pumped out of the ascending limb of the loop could either diffuse into the descending limb or remain in the interstitium. In the first case it will increase the concentration of salt in the descending limb directly; in the second case it will cause water to diffuse out of the descending limb into the more concentrated interstitium. In either case the fluid inside the loop of Henle will increase in concentration toward the tip and become dilute again toward the cortex.

*How is the urine concentrated?* During water diuresis, when antidiuretic hormone (ADH) is absent from the blood, fluid in the distal convolutions remains dilute.[4] The distal convoluted tubule and probably also the collecting duct show low permeability to water under these conditions. On the other hand, when the animal is producing a concentrated urine, and ADH is present, the distal tubule and collecting duct are more permeable to water. Water diffuses out, and the total volume of fluid in the tubule is diminished to about one fifteenth to one twentieth of the volume of the filtrate.[16] By the time the fluid reaches the collecting duct it is isotonic to the blood. Now this small volume of isotonic fluid passes down through the increasingly more concentrated regions of the medulla. Water will diffuse out of the collecting ducts into the interstitium, and the fluid in the collecting ducts will attain the same osmotic concentration as that in the surrounding tissue and as the fluid in the capillaries and loops of Henle. The water that diffuses out of the collecting ducts is carried away by the vasa recta, together with some of the salt deposited in the tissue by the ascending limbs of the loops of Henle.

The maximum concentration that can be achieved by a countercurrent multiplier system depends primarily on three factors: the relative lengths of the multiplier system, the concentration difference between the two limbs, and the rate of flow through the system. The maximum concentration is directly related to the two first factors, but inversely related to the square of the rate of flow. Since the maximum concentration depends on the length of the multiplier system, we should expect to find a correlation between the length of the part of the loop of Henle that acts as a multiplier system and the ability of the animal to concentrate the urine. If only the outer zone of the medulla were active, a thick inner zone should not appreciably increase the concentrating ability. If, on the other hand, the entire medulla acts as a multiplier system, one should expect the concentrating ability of the animal to be related to the combined thickness of the outer and inner zones of the medulla.

In Fig. 3, data on maximal concentrating ability from a number of animals are shown.[17] It is seen that there is a rough correlation between the relative thickness of the medulla and the maximal ability to concentrate the urine. In the upper graph, the maximal ability to concentrate electrolytes and urea are plotted individually against the relative thickness of the medulla. The correlation between the thickness of the medulla and the ability to concentrate

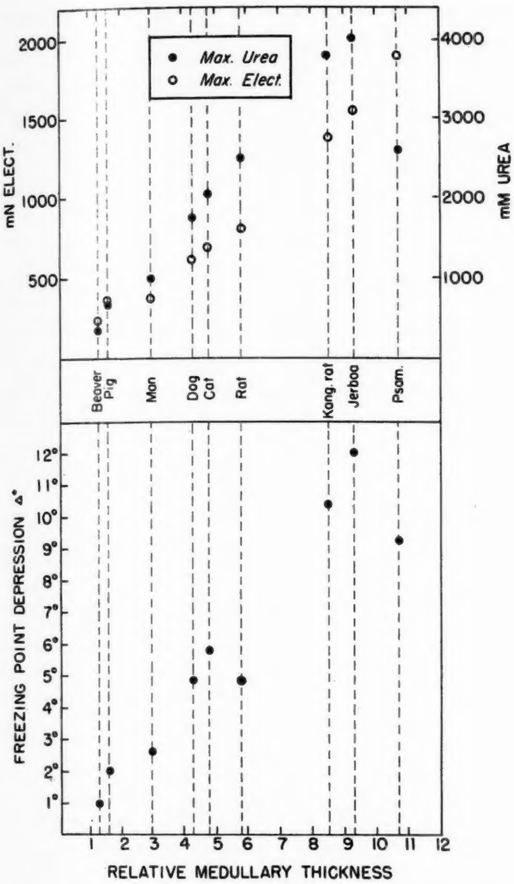


Fig. 3. *Lower graph.* The maximal urinary concentrations obtained in the different animals are given as freezing point depressions and are plotted against the relative medullary thickness of the kidneys. The figures for the relative medullary thickness are taken from Sperber[21] who defines it as follows: $\frac{\text{The medullary thickness} \times 10}{\text{kidney size}}$, where kidney size = the cube root of the product of the dimensions of the kidney. *Upper graph.* The maximal urinary concentrations of urea and total electrolytes are plotted against the relative medullary thickness. The values for maximal urea and electrolyte concentrations were not obtained in the same samples of urine. (From American Journal of Physiology 200:1119, 1961.)

electrolytes is very good indeed. The ability to concentrate urea seems, however, to vary with other factors. It can be seen that three animals, the pig, the beaver, and the Psammomys, are not able to concentrate urea as well as electrolytes, whereas all the other animals can concentrate urea better than electrolytes. The close correlation between the thickness of the medulla and the ability to concentrate electrolytes seems to indicate that not only the outer zone but also the inner zone acts as a countercurrent multiplier system. Further indications that this is so can be seen from the fact that in animals like the Psammomys with a thick inner zone of the medulla the concentration of sodium continues to increase all the way to the tip of the papilla. Furthermore, it is found by micropunctures of the thin limb of the loop of Henle that the osmolality is lower higher up on the papilla than closer to the tip.[18]

When an animal is making a dilute urine, the osmolality of the medulla is higher than that of the cortex and of the blood, but not nearly so high as in the animal making a concentrated urine. It would seem that the countercurrent multiplier system is operating also when the kidney is producing a dilute urine, but less effectively. If the rate of flow, i.e., the flow through the loops of Henle and the flow through the vasa recta, were increased during high diuresis, one would expect that the maximal concentration that the countercurrent system could set up would be diminished. Therefore, it seems quite possible that the rate of flow should be increased during high diuresis. This was actually found by Thurau, Deetjen and Kramer,[19] in studies in which the blood flow in the renal papilla was measured directly by placing photocells on the medulla. However, Lilienfeld and associates,[20] in their studies with $I^{131}$-labeled protein, came to the opposite conclusion, namely, that during a high flow of urine the flow of blood through the renal papilla is diminished. At the moment, therefore, this question appears to be unsettled.

If we return to the earthworm, the crayfish, and the lower vertebrates, we see that what was shown for these animals, that the fluid becomes hypotonic in the distal tubule by active reabsorption of sodium, is also true of the mammals. In other words, the mammalian renal tubule does the same thing in this regard as the nephridium in the earthworm (Fig. 1). It is only because mammal and bird tubules are bent into loops that they can produce a hypertonic urine, whereas all the other tubules (except the Malpighian tubules) can make only hypotonic or isotonic urine. The fact that this is so is rather remarkable if we look

at it in another way. It appears that no animals except the insects can make the fluid inside the tubule hypertonic by secreting ions into it. In all the other kidneys, sodium can be reabsorbed to make the fluid inside the tubules hypotonic, and water can move out passively to make the fluid inside the tubule isotonic with its surroundings. Thus, it seems that it is impossible for sodium to be actively secreted into the tubules in any kidney (except in insects), from the most primitive kidney in the annelids to the complicated mammalian kidney, because if this were possible, we should expect to find some animals, for example, the marine fish or the terrestrial reptiles, in which the concentration in urine could be at least slightly higher than that in the blood.

With respect to movements of water, these comparative findings seem to indicate that active transport of water out of the renal tubule is impossible, because again, if this were possible, we should expect to find hypertonic urine in some of the animals without a countercurrent multiplier system.

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# Annual influenza vaccination as a lifesaving measure

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Since the onset of the 1957 pandemic of Asian influenza there have been repeated recommendations for influenza vaccination, with special emphasis on individuals with chronic debilitating disease, pregnant women, and those in the older age groups.[1] The recurrence of influenza A2 in epidemic proportions in the winter of 1959-1960, with the associated increased mortality, showed how infrequently these recommendations had been followed. Apparently, most individuals had not yet grasped the seriousness of the disease nor understood that they might die as a result of influenza. In order to increase the number of vaccinees, medical personnel who care for aged or chronically ill persons should offer considerably more encouragement for, and should provide an organized approach to, annual immunization. Hospital and clinic staffs as well as practicing physicians must consider influenza vaccination as an essential phase of management of their "high risk" patients. In addition to preventing about three fourths of the excess cardiovascular-renal and pneumonia complications and deaths due to influenza, hospital operating costs would be reduced, since therapy of a single case of staphylococcal pneumonia could equal the expense of an entire vaccination program.

The general public as well as most physicians are aware that the large influenza pandemics of 1918-1919 and 1957-1958 caused the death of millions of persons throughout the world. It has not been so well appreciated that excess mortality directly associated with outbreaks or epidemics of Type A or B influenza virus can be shown in many of the intervening years. This type of information is compiled continuously by the Epidemiology Branch of the Communicable Disease Center, United States Public Health Service. Also, studies which include the periods 1887-1956 and 1957-1960 have clearly shown the excess mortality due to this disease.[2-5] It was estimated that 86,000 excess deaths occurred during the period from 1957 to 1960 in the United States alone. Of special interest to readers of this JOURNAL was the observation that more than half of these excess deaths occurred in persons with cardiovascular-renal disease, and over two thirds of the total were in those who were 65 years of age and older. This represents a transition since the 1918-1919 epidemic, when 92 per cent of the excess was due to influenza and pneumonia. During the past 10 to 15 years, only a fourth of the deaths have been due to this cause.

Clinical studies have documented the association of rheumatic heart disease and influenza-associated deaths.[6-8] The occurrence of influenza virus pneumonia in patients with mitral stenosis has been frequently noted, and it has been suggested that pulmonary hemodynamic factors may be of significance in pathogenesis.[6] The dangers of influenza to pregnant women

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have also been the subject of clinical observations that have described increased numbers of cases of fatal pneumonia during epidemics.[7,9,10] This is not too surprising since most infectious diseases are more severe during pregnancy. Other conditions that place a patient in the high-risk group include chronic pulmonary disease and metabolic disorders, such as diabetes mellitus.[5]

The following recommendations for vaccination against influenza in the civilian population have been made by the Surgeon General's Advisory Committee on Influenza, July 31, 1961:

Experience with Asian influenza between 1957-1960 has served to re-emphasize that patients in certain disease categories who acquire influenza are at much greater risk of death or severe morbidity than the normal population or patients with miscellaneous diseases. In order to reduce the hazard to patients at high risk, it is recommended that they be immunized with polyvalent influenza vaccine as soon as practicable after September 1, and no later than the beginning of the usual influenza season in late December. Since a 2-week delay in the development of antibodies may be expected, it is important that immunization be carried out before epidemics occur in the area.

The adult dosage recommended by the Advisory Committee for primary immunization is 1.0 c.c. (500 CCA units) of polyvalent vaccine administered subcutaneously. It is urged that persons who have not previously been immunized should also receive, if feasible, a second dose of 1.0 c.c., approximately 2 months after the first injection. This second dose will serve to protect the small but significant proportion who do not develop adequate antibody after the first injection. Persons previously immunized should be reinoculated with a single booster dose of 1.0 c.c. subcutaneously each year.

Patients in the following disease categories have experienced the highest mortality rates, and, therefore, specific protection is clearly indicated for them as a routine practice:

A. Persons at all ages who suffer from chronic debilitating disease, e.g., chronic cardiovascular, pulmonary, renal, or metabolic disorders; in particular: (1) patients with rheumatic heart disease, especially those with mitral stenosis; (2) patients with other cardiovascular disorders, such as arteriosclerotic heart disease and hypertension, especially those with evidence of frank or incipient cardiac insufficiency; (3) patients with chronic bronchopulmonary disease, for example, chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, pulmonary tuberculosis; (4) patients with diabetes mellitus; (5) patients with Addison's disease.

B. Pregnant women.

C. All persons over 65 years of age.

In years of expected high incidence, vaccination *is recommended* for the following groups of people: (1) persons in medical and health services, public safety, public utilities, transportation, education, and communications; (2) persons in age groups in which influenza occurs in highest incidence, namely, 5 to 25 years.

## Dose and schedule of vaccination by age

1. *Adults (i.e., individuals 13 years of age or older)*. A dose of 1.0 c.c. (500 CCA units) should be administered subcutaneously as soon as practicable after September 1, and no later than January 1. Those not previously immunized should receive, if feasible, a second dose of 1.0 c.c., approximately 2 months after the first injection.

2. *Children aged 6 to 12 years.* A dose of 0.5 c.c. (250 CCA units) should be administered subcutaneously as soon as practicable after September 1, and no later than January 1. Those not previously immunized should receive, if feasible, a second dose of 0.5 c.c., approximately 2 months after the first injection.

3. *Children 3 months old to preschool age.* Initial doses of 0.1 to 0.2 ml. (50 to 100 CCA units) should be administered subcutaneously on two occasions, separated by intervals of 1 or 2 weeks. A "booster" inoculation of the same strength should be given, if feasible, 2 to 3 months later. Preferably, the schedule of vaccination should be completed by January 1. Since febrile reactions to vaccine in this age group may reach an incidence of 20 per cent, it is suggested, when not contra-

indicated, that acetylsalicylic acid (one grain per year of age) be given every 6 hours for the first 24 hours.

4. *Persons previously immunized with polyvalent vaccine.* Each fall, prior to January 1, persons previously immunized with polyvalent influenza virus vaccine should be reinoculated with a single dose according to the following schedule: children 3 months old to preschool age—0.1 to 0.2 ml.; children aged 6 to 12 years—0.5 ml.; adults—1 ml.

Except to warn against the serious consequences of influenza in the high-risk group, it should not be necessary to recommend repeatedly a vaccine that has been of value in military and industrial populations for many years.[11,12] In addition to preventing morbidity from the illness or complications, and occasional deaths in these groups and even in children, the question of permanent damage to the cardiovascular system and cellular metaplasia in the tracheobronchial epithelium needs much more consideration.[13,14] Physiologic abnormalities can be readily demonstrated during the acute phase of influenza by electrocardiography, spatial vectorcardiography, and digital rheoplethysmography.[15,16] Information on the degree of permanent residual changes, if any, in the heart and blood vessels and the bronchial epithelium is certainly needed for influenza as well as other common respiratory illnesses. Perhaps a considerable lengthening of the lifespan could be achieved by eliminating these illnesses.

Even though there is sufficient justification for administration of influenza vaccine to all individuals on an annual basis, the cost, inconvenience, and voluntary behavior of most of the population makes this degree of refinement in the practice of preventive medicine unlikely for the immediate present. The threat of an impending epidemic can serve to stimulate interest in vaccination, but accurate predictions cannot be made often enough. Other incentives in the form of additional viruses, such as adenoviruses or parainfluenza 1,[17,18] sometimes make immunization more desirable by providing a hope, although not based on data, for elimination of all respiratory illnesses during the approaching season. An adequate all-purpose respiratory disease vaccine which contains all the major viruses undoubtedly would solve many of these problems by virtue of its selling features, but progress has been slow on such a preparation. Perhaps the use of adjuvant preparations will allow more viruses to be combined in a single injection, with longer lasting antibody titers. Until these vaccines of the future are demanded by an enlightened population, it behooves all of us to do what is necessary to apply an efficacious vaccine to the prevention of the most serious of the respiratory illnesses, influenza.

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# Clinical communications

## Congenital pulmonary atresia with intact ventricular septum Clinicopathologic correlation of two anatomic types

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Congenital atresia of the pulmonary valve with intact ventricular septum, although a fairly infrequent malformation, is by no means rare. Peacock,[1] in 1871, stated that he had knowledge of 8 or 9 such cases. Abbott[2] included the description of 10 cases in her atlas. Keith and associates[3] mentioned 24 patients with this malformation who were seen at the Hospital for Sick Children, in Toronto.

Most of the case reports have emphasized the presence of a diminutive right ventricle with thick muscular walls or an absence of the right ventricle.[4-10] In 1950, Glaboff and co-workers[11] reported a case which was characterized by a dilated right ventricular chamber, and mentioned that, to their knowledge, only one other similar anomaly had been reported in the literature, namely, a case cited in Abbott's atlas.

In 1956, Greenwold and associates[12] presented evidence which correlated each anatomic type with its specific electrocardiographic and radiologic pattern; they also emphasized the importance of accurate diagnosis of those cases in which a normal or large right ventricular chamber was present, because of the potential for surgical correction or palliation in such instances.

It is the purpose of this paper to report the essential clinical and pathologic features in 20 cases observed at necropsy, to distinguish further the electrocardiographic and roentgenologic features of one group when contrasted with those of the other, and to emphasize the possibility of direct surgical treatment when a right ventricle of normal or larger size is present.

### Material

The heart collection of the Mayo Clinic (approximately 800 specimens) contains 20 hearts with atresia of the pulmonary valve and an intact ventricular septum. This anatomic material was reviewed, together with the clinical histories, roentgenograms, electrocardiograms, and laboratory data. These hearts include the one described by Williams and associates,[13] in 1951, and

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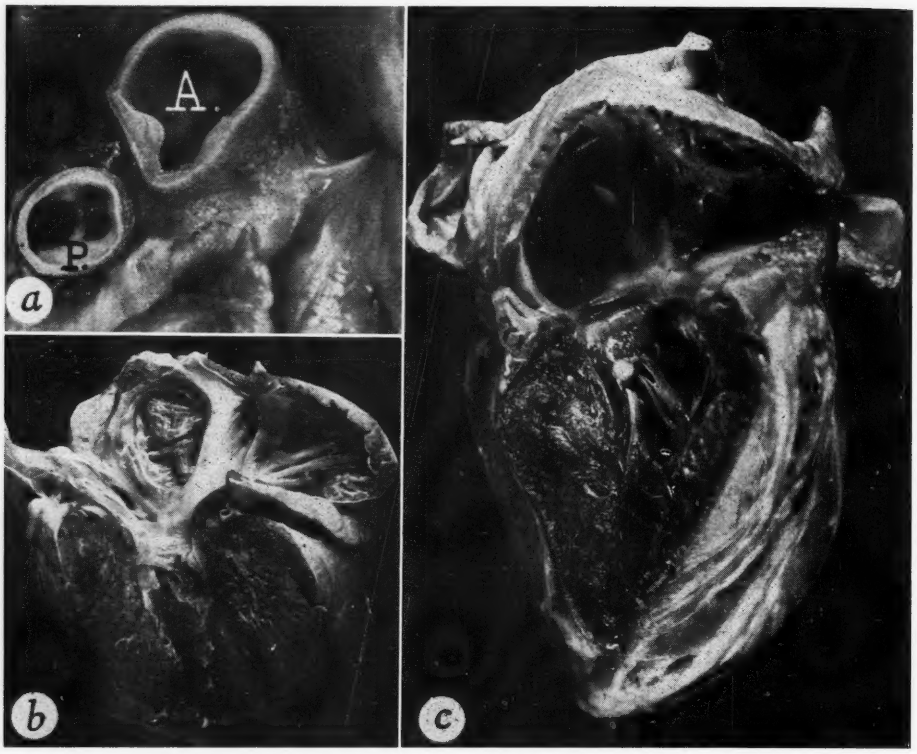


Fig. *1*. Congenital pulmonary atresia with intact ventricular septum and small right ventricular cavity (Type 1). *a*, Pulmonary artery (*P.*) and aorta (*A.*) in Case I. The fused commissures of the atretic pulmonary valve are clearly seen. The diameter of the pulmonary artery is about half that of the aorta. *b*, Case VI, showing the tiny right ventricular cavity and thick ventricular walls, the small but normally formed tricuspid valve, and the fairly large right atrium. (Reproduced with the kind permission of the publisher, Charles C Thomas, from *An Atlas of Congenital Anomalies of the Heart and Great Vessels*, ed. 2, 1954, by J. E. Edwards and associates.) *c*, Case I, showing the small right ventricular chamber.

those mentioned by Greenwold and coworkers.[12] Ten specimens, most of them accompanied by clinical, radiologic, and electrocardiographic data, have been sent for examination to one of us (Edwards) by physicians outside the Clinic.*

**Anatomic features**

Nineteen of the hearts were available for current review; another one had been returned to the sender, but the description and photographs of the specimen made at the time of the initial examination were available for study.

The most striking finding, as already mentioned, was the obvious division of the specimens into two categories, namely, those with a small or tiny right ventricular cavity (hereinafter designated as Type 1), and those with a normal-sized or large right ventricular cavity (Type 2). Thirteen hearts were Type 1, and 7 were Type 2. For reasons to be discussed, one heart with a normal-sized ventricle was considered to be Type 1.

By the term *atresia* we mean the absence of any opening whatsoever. In all of the cases which form the basis of this report, atresia was present at the level of the pulmonary valve. They are to be distinguished from those cases in which the pulmonary valvular obstruction is associated with some opening, however small. The latter situation is designated as *pulmonary stenosis*.

*Pulmonary valve and pulmonary trunk.* In all cases of pulmonary atresia with intact ventricular septum reported herein the obstruction was at the level of the valve. The pulmonary valve was represented by an imperforate fibrous membrane which

*For acknowledgment, see page 602.

measured approximately 2 to 3 mm. in diameter, and which was, at times, dome shaped (Fig. 1,*a*). Along the pulmonary face of the membrane, three equidistant raphes radiated from the center to the periphery of the membrane. The valve in these cases bore a striking resemblance to that in congenital pulmonary valvular stenosis, except, of course, for the absence of an opening at this level.

The pulmonary trunk was narrower than the aorta in all cases; it varied from a diameter which approached that of the aorta to one which was half the size of the aorta. At its origin it had a peculiar funnel-shaped appearance—extremely narrow at the valve and widened peripherally.

*Right ventricle.* In cases of Type 1 heart the right ventricular chamber could be described, with one exception, as either small or tiny, and it stood out in great contrast to the usual tremendous hypertrophy of the wall of this chamber (Fig. 1, *b* and *c*). In one case an organized thrombus filled the entire right ventricular cavity, and another thrombus obliterated the pulmonary trunk.

Nine hearts showed anomalous coronary vessels coursing between the right ventricular chamber and the coronary arteries. A small dimple was present on the surface of the epicardium where these anomalous vessels entered the epicardium. Within the muscle the anomalous vessels arose from sinusoids which were present in the right ventricular wall and communicated with the right ventricular cavity (Fig. 2). These vessels are said to be embryologic channels which persist because the extreme right ventricular pressure forces blood through them.[13] One heart with a right ventricular cavity of normal size was classified as Type 1 because of the presence of an anomalous coronary vessel.

In Type 2 hearts, the less common form, the right ventricular chamber was usually of normal size (Fig. 3, *a* and *b*). The wall was thicker than normal, but the disproportion between the size of the wall and the cavity which was characteristic of Type 1 was not evident. The right ventricle in Type 2 hearts had a general appearance similar to that of hearts in which there was pulmonary stenosis with intact ventricular septum. None of these hearts showed the muscular infundibular stenosis that may be present in some instances of pulmonary valvular stenosis. In 3 cases the right ventricular cavity was larger than normal (Fig. 3, *c*).

*Tricuspid valve.* A striking and perhaps basic difference was shown by the tricuspid valve in the two types. The tricuspid valve in the Type 1 heart was tiny and in keeping with the size of the right ventricular chamber (Fig. 1, *b* and *c*). Despite its small size, the valve had the usual valvular and chordal components, and it appeared to be competent. In one case, in which fluid

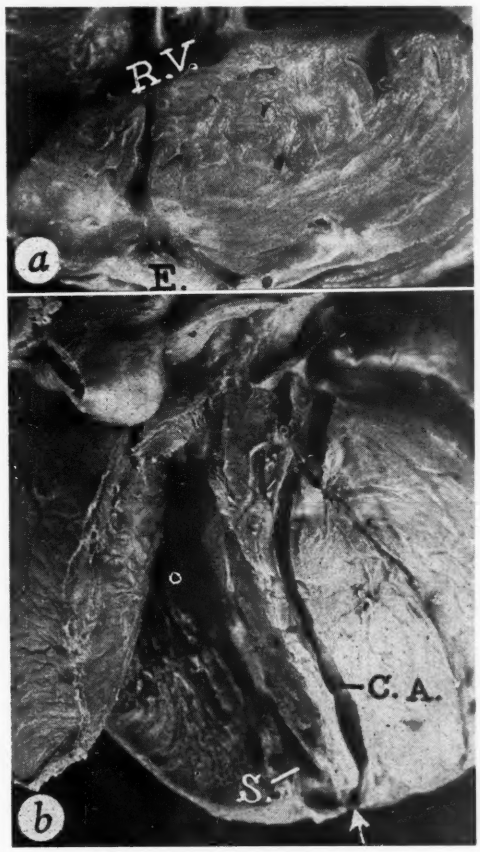


Fig. 2. Anomalous communication of right ventricle with branches of coronary arteries in 2 patients with small right ventricular chambers and apparently competent tricuspid valves. *a*, Specimen from a 3-month-old infant, showing cross section through right ventricular wall and a large intramyocardial sinusoid. The latter extends from the right ventricular cavity (*R.V.*) to the epicardium (*E.*), where it communicates with branches of the coronary arteries. *b*, From a 43-day-old infant. A large sinusoid (*S.*) that communicates with the right ventricular cavity leaves the right ventricular myocardium and, at the apex, joins the anterior descending coronary artery (*C.A.*) at the arrow.

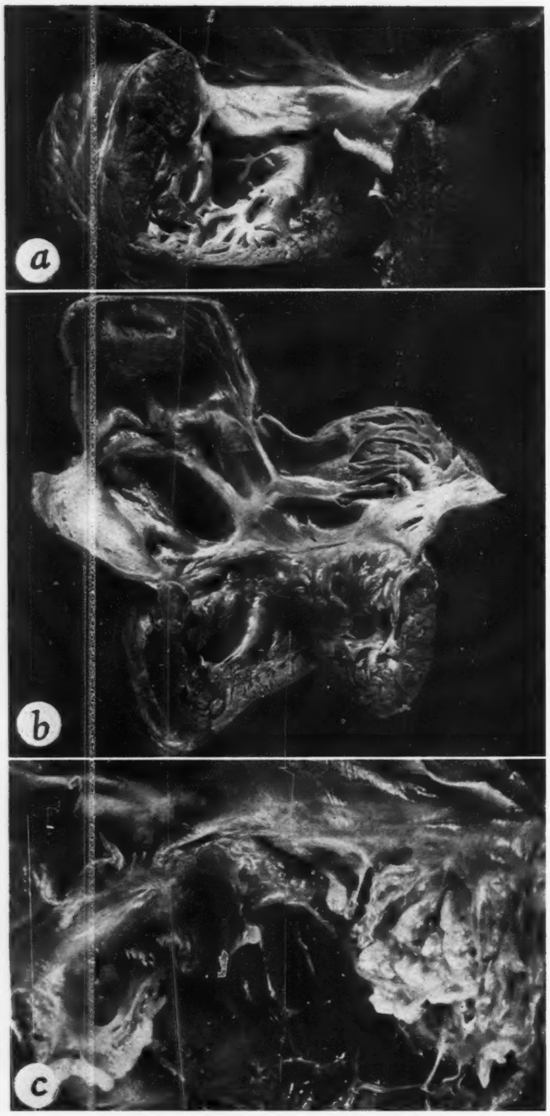

Fig. *3*. Congenital pulmonary atresia with intact ventricular septum and normal-sized right ventricular cavity (Type 2). *a*, Case IX, showing normal-sized right ventricle and malformed tricuspid valve with thickened and shortened leaflets and chordae tendineae. *b*, Case X, showing normal-sized right ventricle and large right atrium, with low insertion of septal leaflet of tricuspid valve. (Reproduced with the kind permission of the publisher, Charles C Thomas, from Edwards, J. E., in Gould's *Pathology of the Heart*, ed. 2, 1960). *c*, Case VII, with huge right ventricle. Note the malformed tricuspid valve, with partial fusion of the posterior and septal leaflets to the ventricular septal wall (see Fig. 3,*d*).

was injected into the right ventricular chamber, the tricuspid valve was shown to be competent.

In Type 2 hearts the circumference of the tricuspid orifice corresponded to the size of the right ventricular chamber. In every case but one the anatomic evidence suggested valvular incompetence. The malformations which affected the tricuspid valve in these 6 hearts were of two main types. Three hearts had nonspecific shortening of the chordae tendineae and leaflets of the tricuspid valve (Fig. 3, *a*). In one of these 3 cases the edges of the leaflets were rolled and thickened; in another the chordae to the anterior leaflet were fused in a conglomeration of fibrous tissue before joining the papillary muscle. In 3 hearts the tricuspid valve showed disturbances in development which bore some resemblance to those seen in Ebstein's malformation (Fig. 3, *b-d*). In one of these specimens, for instance, the posterior leaflet took origin not from the annulus fibrosus but from the right ventricular wall; above this anomalous attachment, and still below the tricuspid annulus, some fibrous valve-like tissue was attached both proximally

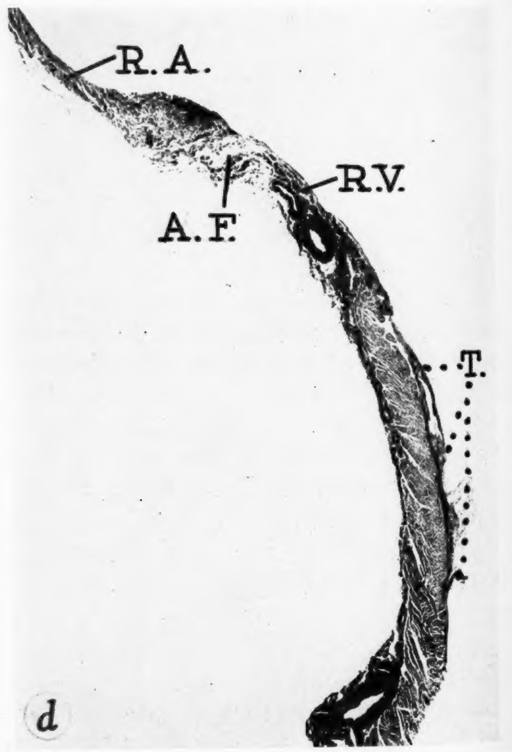


Fig. *3d*. Case VII, showing attachment of the abnormal posterior tricuspid leaflet to the right ventricular wall. *R.A.*, Right atrial wall. *A.F.*, Tricuspid annulus fibrosus. *R.V.*, Right ventricular wall. *T.*, Posterior leaflet of tricuspid valve, making several attachments to the right ventricular wall, each a considerable distance inferior to the annulus fibrosus (elastic-tissue stain; ×4).

and distally to the right ventricular wall. The septal leaflet of the tricuspid valve in this case was composed of translucent soft tissue that did not completely fill the space between facing ends of the anterior and posterior leaflets. The other two hearts had similar malformations except for minor variations.

*Right atrium.* In all cases the vena cava and coronary sinus were properly placed, and the right atrial wall was somewhat thicker than normal. An important difference existed in the two types in that the right atrial chamber of the Type 1 heart was somewhat enlarged, whereas the enlargement in the Type 2 heart was, generally, of striking proportion (Fig. 3, *b*).

*Atrial septum.* An interatrial communication was present in all cases—a foramen ovale with a competent valve in 16 instances, and an atrial septal defect in 4.

*Left side of heart and aorta.* The left side of the heart was normal save for somewhat larger dimensions of the chambers and valves. All hearts suggested an increased thickening of the left ventricular wall. The aortic valve was normal, and the coronary arteries arose normally. The ascending aorta and the pulmonary trunk were interrelated in the usual fashion. The aorta appeared to be a little larger than normal. In each case the aortic arch was on the left side.

*Ductus arteriosus.* In each specimen which included the ductus arteriosus, this vessel was patent. Often, however, the ductus had a cordlike feel and appeared to be undergoing normal postnatal anatomic obliteration of its lumen. Two specimens showed a thrombosis of the pulmonary end of the ductus, which caused partial occlusion in one and complete occlusion in the other.

*Pulmonary vasculature.* The pulmonary arterial tree in instances of pulmonary atresia is of interest because the muscular pulmonary arteries in most cases show pronounced thinning of the media when compared with pulmonary vessels of normal infants of the same age group. This is especially true when the ductus arteriosus is relatively long and narrow. Calculation of the ratio between medial tissue and pulmonary parenchyma suggests that this diminished thickness is caused by atrophy rather than by dilatation of the arteries.[14]

## Clinical features

*Sex.* The sex was recorded in 17 cases; there were 6 females and 11 males.

*Clinical history.* A clinical history was available in 16 cases. Cyanosis was the most remarkable and constant clinical feature; it was noted during the first 24 hours of life in 15 patients, and at 48 hours in 1 patient. Except for 2 patients in whom it was severe, cyanosis was usually of a mild degree at rest, increased greatly with feeding or crying, and improved—sometimes to the point of disappearance—with the administration of oxygen. Dyspnea was a feature in most patients at one time or another.

*Physical examination.* Two patients had a systolic thrill at the left lower sternal border; these 2 patients had a Type 2 heart, and both had a severely malformed tricuspid valve. All but 3 patients had a systolic murmur of variable intensity, which was heard mostly at the left lower sternal border; in 3 patients this murmur had disappeared shortly before death. One patient also had a continuous murmur of moderate intensity at the left upper sternal border. The second sound, when mentioned, was described as single, loud, and clicking, in most instances; it was split in one patient, and questionably split in another.

The liver was of normal size at the time of the initial examination, except in one child with a Type 1 heart who died at the age of 8 days, and in whom a nonpulsating liver was palpable 2 fingerbreadths below the costal margin. In a few patients the liver enlarged shortly before death.

The lungs were clear to auscultation in all but 2 patients. In one of these patients, râles were noted on the first day of life but disappeared rapidly; in the other patient, râles were heard during the last day of life.

Except for the presence of the aforementioned thrill at the left lower sternal border in 2 patients with a Type 2 heart, possibly caused by tricuspid insufficiency, there was no distinctive clinical feature which characterized one group so that it could be distinguished from the other.

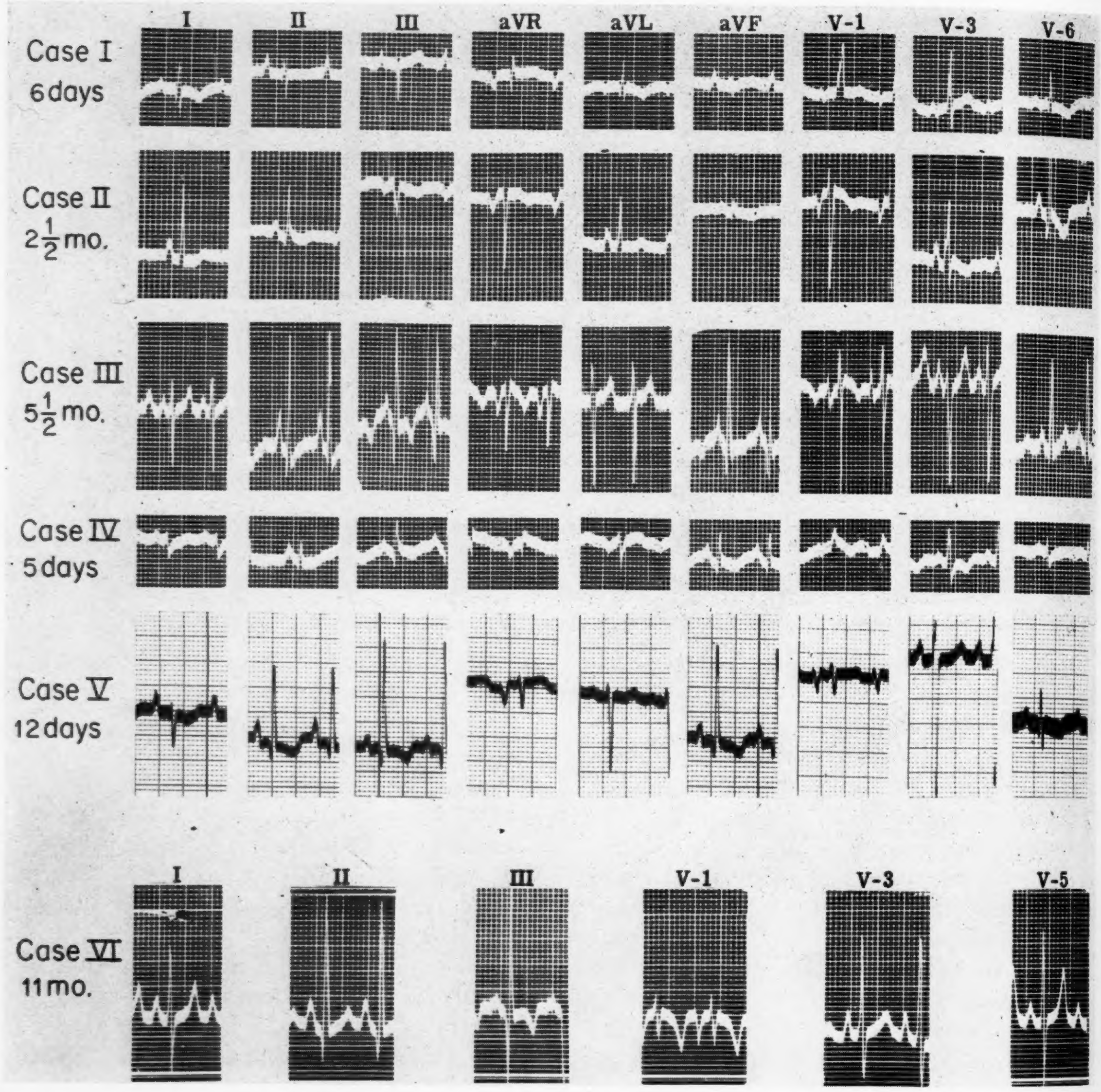


Fig. 4. Electrocardiograms in cases of Type 1. Tracings from patients who were more than 1 week of age show left ventricular dominance, evidence of atrial enlargement, and a small or absent R wave in Lead aVR.

*Oximetry.* Ear oximetry was done in 3 patients (Table I). The oxygen saturation at rest ranged from 60 to 65 per cent, and decreased considerably after exercise in one patient. The saturation increased slightly in 2 patients who breathed oxygen during oximetry.

*Mode of death.* The age at death was known in 18 cases; it ranged between 2 days and 11 months. Sixteen patients died when they were less than 6 months old, 13 when they were less than 3 months old, and 4 during the first week of life. No significant difference was noted between the two groups (Types 1 and 2) in so far as the age at death was concerned.

In the great majority of cases, death came rapidly and unexpectedly, most often during an episode of increased cyanosis and dyspnea. A few infants showed the classic picture of congestive heart failure, with a liver which enlarged shortly before death. Two patients (one with a Type 1 heart and one with a Type 2 heart) died shortly after a Brock valvulotomy. In another case, a procedure to produce a shunt was planned, but the patient died at the beginning of the operation. Acute pyelonephritis was the precipitating factor in the death of another patient.

Associated malformations or defects, including esophageal atresia, imperforate

anus, and Mongolism, were found in 3 patients; none of these conditions was the precipitating cause of death.

## Electrocardiographic aspects

The electrocardiogram was available for review in 10 cases, including 6 cases of Type 1 and 4 of Type 2. The tracings were evaluated according to our experience with various types of congenital heart disease relative to right and left ventricular overload,[15] atrial enlargement, and the direction of the ventricular depolarization vector in the frontal plane.[16]

In patients who were more than 1 week of age a significant correlation with the anatomic findings was found, which apparently reflected the hemodynamic situation before death.

Four patients of Type 1 who were more than 1 week of age showed atrial enlargement and left ventricular dominance for age (Cases II, III, V, and VI in Fig. 4). In 2 of these patients the mean manifest electrical axis of the QRS complex was +110 degrees; in the other 2 it was +15 and +90 degrees, respectively. In 2 other patients with a Type 1 heart, both of whom were less than 1 week of age, the electrocardiogram was atypical, showing an axis of −10 degrees at 24 hours and −30 degrees at 6 days, atrial enlargement and right ventricular overload in one (Fig. 4, Case I), and an axis of +110 degrees, some atrial enlargement, and normal ventricular complexes in the other (Fig. 4, Case IV).

Three patients with a Type 2 heart who had electrocardiograms taken at 13 days and 6 weeks in one, and at 14 days and 7 weeks, respectively, in the other two, showed an axis between +105 and +145 degrees, atrial enlargement, and right ventricular overload. All three had q waves in Lead $V_1$. One also showed evidence of good left ventricular potential (Fig. 5, Case IX). Another patient with a Type 2 heart who died at the age of 2 days had an atypical tracing which showed some atrial

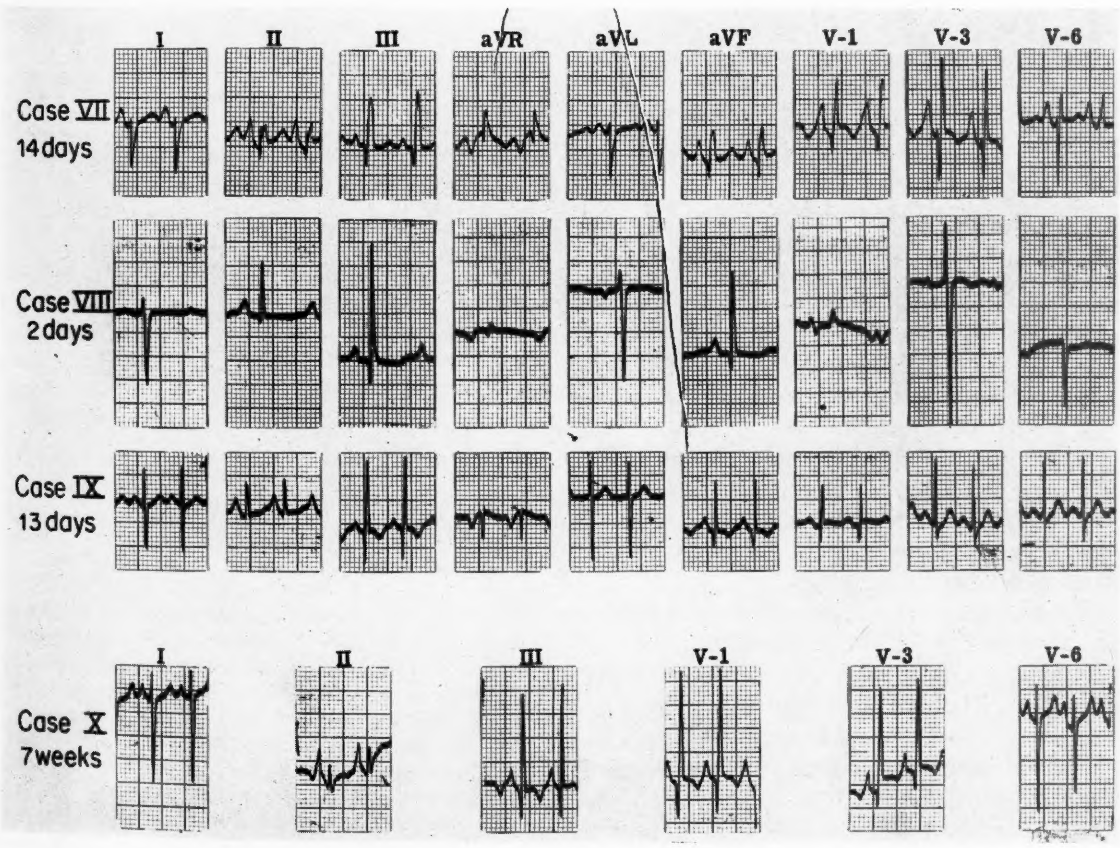


Fig. 5. Electrocardiograms in cases of Type 2. Note the presence of a qR pattern in Lead $V_1$ and tall peaked P waves in Cases VII, IX, and X. The changes are interpreted as resulting from right ventricular hypertrophy.

*Table* I. *Arterial oxygen saturation (per cent) measured by ear oximetry in congenital pulmonary atresia with intact ventricular septum: three cases*

| Case | Type | Breathing air | | Breathing oxygen | |
|---|---|---|---|---|---|
| | | Rest | Exercise | Rest | Exercise |
| VII | 2 | 65 | Stable | — | — |
| VIII | 2 | 60 | 57 | 70 | — |
| VI | 1 | 64 | 38 | 74 | 28 |

enlargement and an axis of +120 degrees (Fig. 5, Case VIII). All of these patients had malformed tricuspid valves.

All except one patient had a clockwise QRS vector loop in the frontal plane, with the main area of the loop below the horizontal. In Case I the loop was counterclockwise, with its main mass in the quadrant extending from 0 to −90 degrees.

### Roentgenographic aspects

Posteroanterior roentgenograms of the thorax were available for review in 11 cases, which included 8 of Type 1 and 3 of Type 2 (Fig. 6). The pulmonary vascularity was decreased in all instances. In most cases the difference between the two anatomic types was obvious. In general, Type 1 patients had hearts of normal or moderately increased size, with a normal right border (Fig. 6, *a-i*). Infants who died when they were less than 1 week of age tended to have larger hearts (Fig. 6, *d*, *e*, and *h*). In most patients the region of the main pulmonary artery was concave, with the apex downward and to the left.

Type 2 patients had grossly enlarged hearts, with prominence of the right border (Fig. 6, *j-l*).

When serial roentgenograms were made, both types showed progressive enlargement of the heart, although the Type 1 hearts never reached the gigantic proportions of certain of the Type 2 hearts.

Special mention should be made here of Case V (Type 1, Fig. 6, *c*), in which the thoracic roentgenogram showed evidence of severe cardiac enlargement, with a contour indistinguishable from that seen in Type 2 hearts. This patient, a 13-day-old boy, was in cardiac failure when this roentgenogram was taken. Necropsy showed this heart to have the largest right atrium of the group and an extremely small patent foramen ovale.

### Angiocardiography

One patient (Case V) underwent selective angiocardiography. The opaque medium was injected successively into the right ventricle and the left atrium. The left atrial injection was not remarkable except that it demonstrated simultaneous filling of the aorta and pulmonary artery through a patent ductus arteriosus. The right ventricular injection demonstrated dilated myocardial sinusoids and anomalous coronary vessels in the wall of the right ventricle (Fig. 7).

### Cardiac Catheterization

The same patient (Case V) also underwent catheterization of the right side of the heart; the results are summarized in Table II.* The left atrium was entered through an interatrial opening. Three curves were obtained after the injection of 5 mg. of Cardio-Green. Indicator-dilution curves were recorded at the femoral artery after injection of Cardio-Green into the inferior vena cava, the right atrium, and the right ventricle. All three curves were similar in shape; they showed appearance times of 3 to 5 seconds, and large initial deflections with extremely slow clearance of dye from the circulation. These curves were thought to indicate the presence of an extremely large right-to-left shunt; the close similarity between the curves from the right side of the heart

*Table* II. *Data on cardiac catheterization in Case V*

| Site | Pressure (mm. Hg) | $O_2$ saturation (%), by cuvette oximeter |
|---|---|---|
| Superior vena cava | 13/3 | 31 |
| Inferior vena cava | 11/3 | 24 to 43 |
| Right atrium | — | 35 |
| Right ventricle | 137/10 | 42 |
| Left atrium | 17/11 | 73 |
| Femoral artery | 85/42 | 74 |

*Cardiac catheterization was performed by Dr. H. J. C. Swan.

and those from the left atrium suggested that a common route of egress to the systemic circuit existed.

**Comment**

In patients with pulmonary atresia and intact ventricular septum who present a

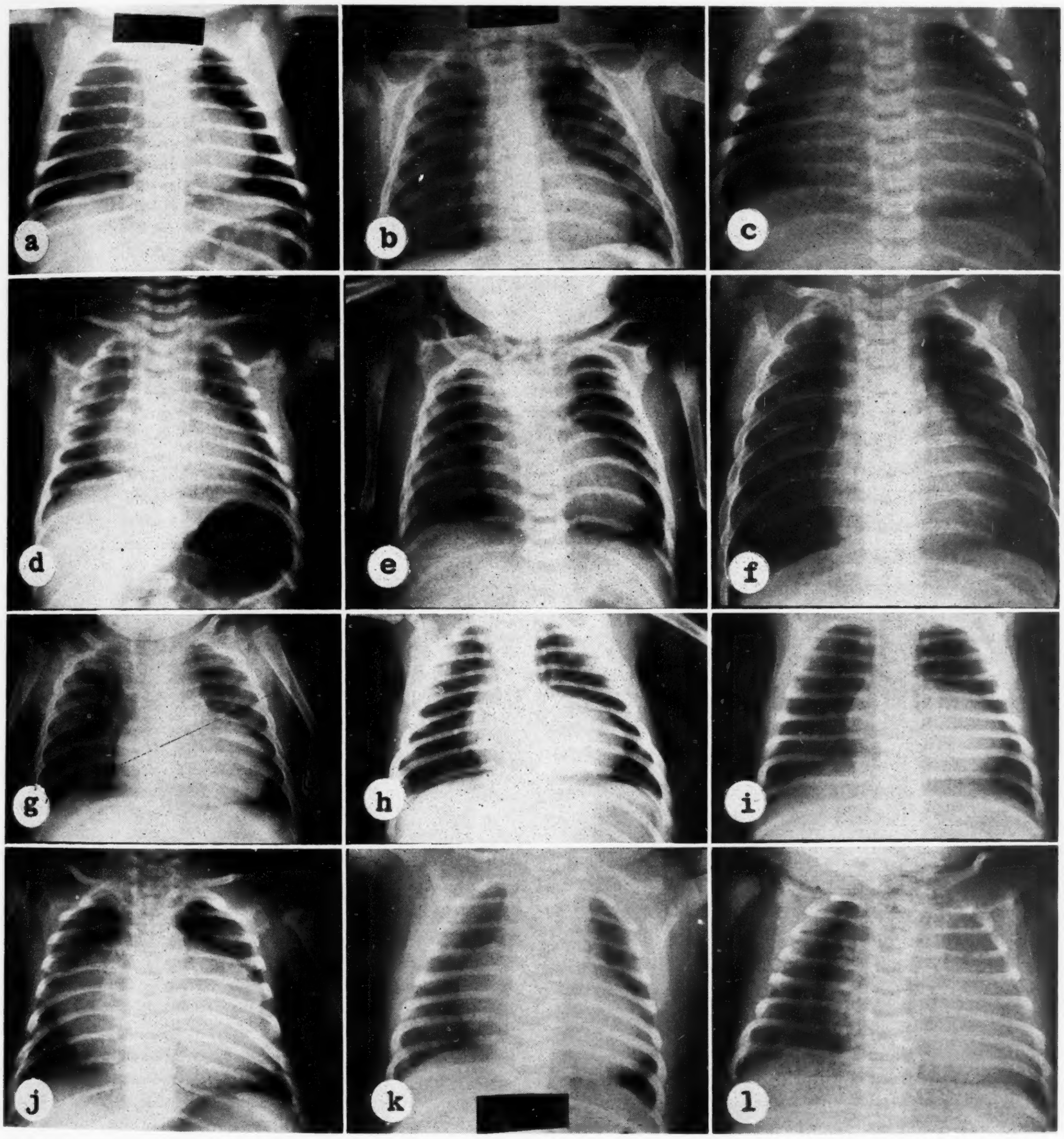


Fig. *6*. Thoracic roentgenograms in patients with pulmonary atresia and intact ventricular septum. *a-i*, Type 1; *j-l*, Type 2. Unless otherwise specified, these roentgenograms were made a few days before death. *a* and *b*, Case XII, taken at 1 month and 5 months of age, respectively. Note the progressive but moderate cardiac enlargement. *c*, Case V, taken at 13 days of age. This patient had an extremely small interatrial communication and the largest right atrium of this group. *d*, Case IV, taken at 3 days of age. This patient had a right ventricle of normal size, but the heart was classified as Type 1 because of the presence of anomalous coronary vessels emanating from the right ventricle, and a normally formed tricuspid valve. Note the prominence of the right atrial shadow. *e*, Case II, taken at 3 days of age. *f*, Case III, taken at 5 months of age. *g*, Case VI, taken at 11 months of age. (Reproduced with the kind permission of the publisher, Charles C Thomas, from *An Atlas of Congenital Anomalies of the Heart and Great Vessels*, ed 2, 1954, by J. E. Edwards and associates.) *h*, Film from a 3-day-old patient. *i*, Case I, taken at 5 days of age. *j*, Case X, taken at 48 days of age. The patient died 10 days later. (Reproduced with the kind permission of the publisher, Charles C Thomas, from Edwards, J. E., in Gould's *Pathology of the Heart*, ed. 2, 1960.) *k*, Case IX, taken at 11 days of age. The patient died 40 days later, shortly after a Brock procedure. *l*, Case VIII, taken at 1 day of age.


Fig. 7. Case V. Frontal and lateral angiocardiograms in an 18-day-old patient who had pulmonary atresia with intact ventricular septum and small right ventricle. Myocardial sinusoids (*M.S.*) and an anomalous coronary vessel (*C.V.*) are clearly seen. Necropsy revealed that this vessel emptied into the anterior descending coronary artery. This patient died after an unsuccessul Brock procedure.

small right ventricle, the tricuspid valve, although small, appears to be normal in shape and apparently is competent. The right ventricle (Fig. 8), which has no path of egress, hypertrophies concentrically and forces blood through the only possible escape, namely, the embryologic myocardial sinusoids, and this keeps them wide open after birth. Because of its small cavity and thick walls, which offer great resistance to filling, the right ventricle in itself would constitute an obstacle to proper flow should the valvular obstruction be relieved. Opening of the pulmonary valve might not correct the patient's hemodynamics sufficiently to assure survival in the immediate postoperative period. Also, the virtual absence of a right ventricular outflow tract in these cases makes it extremely difficult and hazardous to perform a Brock operation. A procedure to produce a shunt probably would be better in these cases.

On the contrary, 6 of the 7 patients who had right ventricles which were normal in size or enlarged had tricuspid valves that presented gross anatomic malformations which more than likely were severe enough to cause valvular insufficiency. This tricuspid incompetence appears to be responsible for the development of the right ventricle by allowing a ready path of egress for the blood during ventricular systole. The stimulus for anomalous coronary connections does not exist, and we were unable to demonstrate them in any of these patients. This lesion is, we believe, potentially amenable to operation without the use of extracorporeal circulation, as demonstrated in the following case.

*Case IX.* A 7-week-old white boy was admitted to the hospital in June, 1953, with a history of cyanosis and a heart murmur since birth. During the week preceding admission, he had had frequent spells of anoxia, especially at the time of a bowel movement. Examination revealed a severely cyanotic child with clubbing of the fingers and toes, and a harsh systolic murmur with a thrill at the third and fourth left intercostal spaces. The lungs were clear. The liver was felt two fingerbreadths below the right costal margin. The electrocardiogram showed atrial enlargement and right ventricular overload (Fig. 5). The thoracic roentgenogram showed clear lung fields and pronounced cardiac enlargement (Fig. 6). A diagnosis of pulmonic stenosis was made.

Through a transventricular approach, a probe was passed forcibly from the right ventricle into the pulmonary artery, followed by a Potts dilator open to 6 mm. The patient presented an immediate and striking improvement in color and did fairly well for 2 or 3 hours after operation. However, Cheyne-Stokes respiration soon developed, along with an irregular heart rate, and the infant died 5 hours after operation. Necropsy disclosed that the valvotomy had been made at the periphery of the valve and had resulted in only a partially effective opening.

The importance of differentiating clinically between Type 1 and Type 2 hearts

is evident. We believe that this can be done fairly easily in patients who are more than 1 week of age. In a cyanotic child in whom the lungs are clear the presence of a normal-sized or moderately enlarged heart and an electrocardiogram which shows right axis deviation with left ventricular dominance would point toward the diagnosis of pulmonary atresia with intact ventricular septum and a small right ventricle; the right axis deviation differentiates it from tricuspid atresia. Conversely, a similar patient who presented evidence of pronounced enlargement of the heart with right ventricular overload on the electrocardiogram most likely would have a right ventricle of normal size or larger (Type 2).

In patients who are 1 week of age or younger the clinical diagnosis was, in our experience, almost impossible because the electrocardiogram and thoracic roentgenogram were atypical. In one patient the QRS axis was −60 degrees, which fact made the differentiation of this anomaly from tricuspid atresia extremely difficult.

Angiocardiography and cardiac catheterization should be used when the diagnosis is in doubt, but these procedures are not necessary in every case, since the risk from the tests alone is fairly high and the results are not always diagnostic.

Of all the diagnostic procedures available, selective angiocardiography which delineates the right ventricle, when possible to perform, is probably the most valuable. It should help to obtain better information as to the size of the right ventricular cavity, and the demonstration of the abnormal myocardial sinusoids should point to the diagnosis of pulmonary atresia of Type 1. To our knowledge, this is the first time that these anomalous vessels have been demonstrated by angiocardiography. Rapid injection of a relatively large quantity of medium into the right ventricle was probably the main factor in obtaining good visualization of the right ventricle and filling of the sinusoids.

Transitional forms of this anomaly may exist. As already mentioned, one patient had a right ventricle of normal size and a fairly normal tricuspid valve, and was classified as Type 1 mainly because of the presence of anomalous coronary connections; this patient was less than 1 week of age, and the electrocardiogram and thoracic roentgenogram were atypical.

As cases continue to accumulate, the entire spectrum of this anomaly will doubtlessly emerge, the range being from a right ventricle of aneurysmal proportions[2] to one of microscopic size. However, we believe that the pathologic classification into two groups, which has enabled us to properly label 19 of the 20 cases and to correlate the clinical and pathologic findings in most instances, will remain valid.

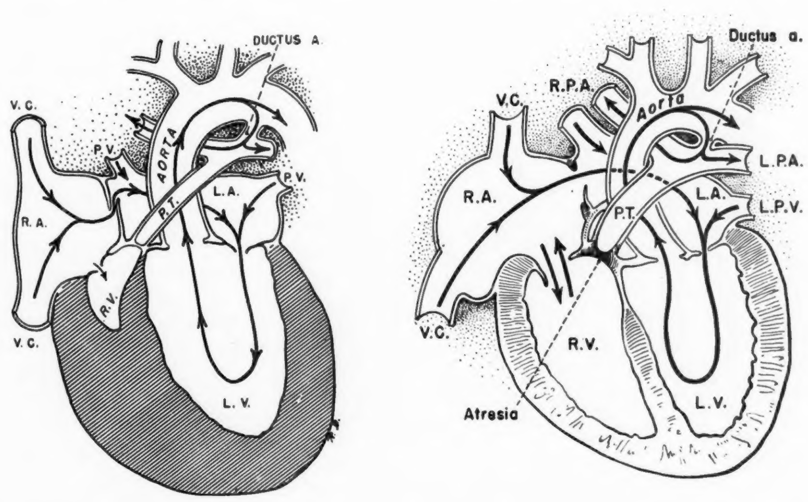


Fig. *8*. Diagram of the circulation in patients with a small right ventricle (*left*) and in those with a right ventricle of normal size or larger and tricuspid insufficiency (*right*). (Reproduced with the kind permission of the publisher, Charles C Thomas, from Edwards, J. E. in Gould's *Pathology of the Heart*, ed. 2, 1960.)

## Summary

A clinical and pathologic study was made in 20 cases of pulmonary atresia with intact ventricular septum proved at necropsy. The hearts usually could be divided readily into two groups, namely, those with a small or tiny right ventricle (Type 1) and those with a right ventricle of normal size or larger (Type 2); 13 hearts were of Type 1, and 7 were of Type 2.

In cases of Type 2 the tricuspid valve presented gross anatomic malformations, namely, nonspecific shortening and thickening of the chordae tendineae and leaflets in 3 instances, and malinsertion of the leaflets in 3 others—a defect similar to that encountered in Ebstein's disease. In cases of Type 1 the tricuspid valve was small but well formed; 9 of these hearts had anomalous coronary vessels which connected the right ventricular myocardial sinusoids with the coronary arterial system.

When the patients were more than 1 week of age, these two types usually could be differentiated on the basis of radiologic and electrocardiographic findings. This is of considerable importance because of the possibility of direct surgical treatment when the right ventricle is of normal size or larger.


For the 10 heart specimens which were received from outside the Clinic, we wish to express our most sincere thanks to the following physicians: Dr. T. E. Ludden, Pomona, Calif.; Dr. G. D. Griffin, Roswell, N. M.; Dr. R. M. Kniseley, Oak Ridge, Tenn.; Dr. J. D. Barger, Phoenix, Ariz.; Dr. Sylvia Johns, San Antonio, Tex.; Dr. E. J. Eichwald, Great Falls, Mont.; Dr. J. B. Maxwell, Alexandria, La.; Dr. C. M. Whorten, Jacksonville, Fla.; Dr. D. L. Alcott, San Jose, Calif.

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# The flat right atrial border

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In 1957, Soloff and Zatuchni[1] described an angiocardiographic sign of constrictive pericarditis. The right lateral border of the opacified right atrium was rigid and had lost its normally outward convexity. This feature of constrictive pericarditis was independently described by Figley and Bagshaw,[2] and was subsequently also demonstrated in negative-contrast roentgenograms employing carbon dioxide.[3] The purpose of this report is to show that such involvement of the right atrium can occur early and is not hemodynamically significant.

## Case report

G. K., a 64-year-old-white man, was admitted to Episcopal Hospital on Jan. 19, 1961, because of chest pain and shortness of breath. A pericardial poudrage had been done by Dr. Thomas J. E. O'Neill on Nov. 17, 1960, because of intractable pain, due to coronary insufficiency, since a "heart attack" in 1949. Prior to operation, cardiac examination by clinical and roentgenologic methods had revealed normal findings. An electrocardiogram showed symmetry of the T waves and slight prolongation of the S-T segment, which was minimally depressed in leads facing the epicardial surface of the left ventricle.

Pericardial poudrage was accomplished through a small incision in the left fifth intercostal space medially. The pericardial cavity was clean, and 5 Gm. of talc were inserted. Postoperatively, the patient's course was uneventful other than for the occurrence of a left pleuritis. Left thoracentesis was performed twice, and serous fluid was obtained. He was discharged on Dec. 6, 1960.

After discharge, he continued to have an ache in the left hemithorax. On the day of readmission, a severe episode of pain occurred. Pain was aggravated by inspiration and was associated with shortness of breath and a sensation of syncope. During hospitalization, he was given analgesics, and the symptoms abated. There was no fever. Examination revealed dullness and decreased breath sounds over the left lower hemithorax posteriorly. There was no cardiac impulse. The heart sounds were normal in quality, rate, and rhythm. The jugular veins were slightly distended but filled more rapidly from above than below, and collapsed with inspiration. There was no pulsus paradoxus. The liver and spleen were not palpable. There was no edema.

Fluoroscopic examination of the chest revealed density in the left lower hemithorax, mainly posteriorly, consistent with pleural effusion. The left hemidiaphragm was elevated and limited in motion. The cardiac silhouette was normal in size and shape. Border pulsations were present throughout. Minimal change in size of the cardiac silhouette occurred with the Valsalva and Müller maneuvers.

Electrocardiographic examination disclosed abnormality only of the T waves. The T vector was directed minus 122 degrees posteriorly. Voltages of the QRS and P complexes were normal and unchanged, as compared with preoperative tracings.

Laboratory studies, including blood count, and transaminase and antistreptolysin titers, were normal.

Antecubital venous pressure was 90 mm., and circulation times with ether and Decholin were 8 and 16 seconds, respectively.

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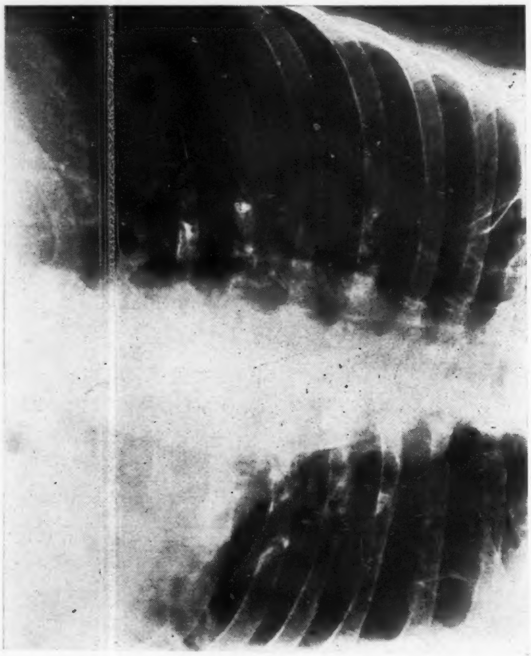

Fig. *1*. Negative-contrast roentgenogram with radiolucency produced by carbon dioxide within the right atrium. Note its flat border. Adjacent density is thicker than in the normal person.

Negative-contrast study of the heart was done on Jan. 25, 1961. One hundred milliliters of carbon dioxide were rapidly injected intravenously, with the patient in the left lateral decubitus position. The lateral border of the cardiac silhouette in the region of the right atrium was convex outward, and the lateral border of the gas shadow was flat (Fig. 1). The density between these two borders was asymmetrically increased to a maximum of 13 mm. at the summit. These findings were interpreted as being due to constrictive pericarditis and effusion.

Cardiac catheterization was performed on Feb. 16, 1961. The oxygen consumption was 155 c.c./min.; arterial oxygen saturation was 92 per cent; and cardiac output was 3.7 L./min. The pressures, in millimeters of mercury, were: right atrium, 6-7 (mean); right ventricle, 25/7; pulmonary artery, 25/10; pulmonary wedge, 9-10 (mean); and brachial artery, 150/80. There was no gradient between the superior vena cava and right atrium, or between the right atrium and right ventricle. The contour of the right atrial pressure pulse was not M or W in shape. The right ventricular pressure pulse showed no diastolic dip, and the ratio of end-diastolic to systolic pressures was less than 1:3. There was, therefore, no hemodynamic evidence of constrictive pericarditis.[4] The slight reduction in cardiac output, and the minimal elevation of end-diastolic pressure in the right ventricle, although not strikingly abnormal, were perhaps due to mild myocardial dysfunction related either to underlying coronary arterial disease or to myocarditis secondary to pericardial poudrage, or to both.

## Discussion

In the normal person, contrast roentgenograms reveal a convexity outward of the border of the right atrium, outlined by gas or opaque media, and adjacent density is no more than 5 mm. thick. Change in convexity or thickness allows for recognition of pericarditis or effusion, or both.[1-3,5]

A flat right atrial border has been seen to occur only in persons with constrictive pericarditis. At operation, this border of the right atrium was found to be intimately linked with the overlying pericardium.[1] In fact, the linkage was such that the surgeon could not find a plane of cleavage. That this so-called structural abnormality is not necessarily a late phenomenon is indicated by the case reported upon here; in this patient it was found 2 months after pericardial poudrage.

The hemodynamic importance of this finding has not been previously determined, although it was originally suggested to have no functional significance.[1] In fact, Isaacs, Carter and Haller[6] found that constriction of the right atrium produced experimentally in dogs resulted in no significant hemodynamic abnormality; and Sawyer and associates,[7] in human beings with constrictive pericarditis, observed no fall in pressure between the superior vena cava and right atrium, or between the right atrium and right ventricle. Their conclusion that constriction of the right atrium by pericarditis is not hemodynamically significant is supported by our findings.

## Summary and conclusions

A case is reported in which negative-contrast roentgenography uncovered a flat, rather than normally convex outward, right atrial border, 2 months after pericardial poudrage. Such a finding, although diagnostically meaningful of structural abnormality, does not necessarily signify hemodynamic abnormality.

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# Correlation between the shape of the P wave and the length of the P-R interval in normal electrocardiograms

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Differences in the shape of the P wave and their correlations with other electrocardiographic elements are indifferently treated in the electrocardiographic literature. Correlations between the shape of the P wave and length of the P-R interval, to the best knowledge of the author, have not yet been investigated. The present study deals with this particular correlation.

The normal P wave in standard leads may present a rounded, a peaked, or, less frequently, a notched form. The relative frequency of differently shaped P waves is estimated very distinctly by different authorities. Shipley and Hallaran[1] found rounded P waves in two thirds and peaked P waves in one third of 200 normal electrocardiograms. Notching along the course of the P wave occurred in about 30 per cent of the tracings. Similarly, Stewart and Manning[2] found that in the electrocardiogram of 500 healthy aviators there was an 83.4 per cent incidence of rounded P waves, whereas peaked and notched P waves were observed with a frequency of 9.8 and 5.4 per cent, respectively. In contrast, Graybiel and associates[3] found a 41.1 per cent incidence of peaked P waves in the electrocardiograms of 1,000 young aviators, and an incidence of 29.4 and 28.2 per cent, respectively, of rounded and notched P waves. These varying shapes of the atrial wave bear different correlations with the length of the P-R interval, as the present study demonstrates.

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## Methods and materials

Normal records inscribed with a Sanborn Cardiette were used for purposes of the present investigation. The P wave, the P-R interval, and the P-R segment were examined in Lead II only. The duration of the P-R segment was calculated by substracting the duration of the P wave from the length of the P-R interval. P waves were classed according to their shape into three groups: (1) peaked, (2) rounded, and (3) notched. A peaked P wave was considered to be present when the acutely pointed apex lasted not more than 0.01 second. Only records which exhibited P waves of constant form were used.

Normal records which exhibited P-R intervals that were from 0.11 to 0.24 second in duration were used in the present investigation. It is generally agreed that the commonly observed upper limit of the normal P-R interval is 0.20 second. However, the general consensus is that the P-R interval may often last as long as 0.24 second or more, in the absence of any other electrocardiographic evidence of a diseased myocardium. Thus, to extend the present correlative study to the extreme limits of duration of the P-R interval, records with a P-R interval up to 0.24 second were considered to be nor-

*Table I. Correlation between the shape of the P wave and the length of the P-R interval, duration of the P wave, P-R segment, and the ratio P/P-R segment*

| | *Incidence of P wave* | | | |
|---|---|---|---|---|
| | *Rounded* (%) *56.2* | *Peaked* (%) *38.8* | *Notched* (%) *5.0* | *Total* *100.0* |
| P-R interval (sec.) | 0.202 ± 0.021 | 0.134 ± 0.023 | 0.192 ± 0.025 | 0.171 ± 0.037 |
| Range | 0.11 – 0.24 | 0.11 – 0.22 | 0.17 – 0.23 | 0.11 – 0.24 |
| P duration (sec.) | 0.101 ± 0.014 | 0.086 ± 0.013 | 0.103 ± 0.011 | 0.095 ± 0.015 |
| Range | 0.07 – 0.12 | 0.05 – 0.12 | 0.08 – 0.12 | 0.05 – 0.12 |
| P-R segment (sec.) | 0.093 ± 0.028 | 0.048 ± 0.019 | 0.089 ± 0.026 | 0.075 ± 0.031 |
| Range | 0.03 – 0.16 | 0.01 – 0.10 | 0.05 – 0.13 | 0.01 – 0.16 |
| Ratio P/P-R segment | 1.17 ± 0.30 | 1.76 ± 1.69 | 1.16 ± 0.47 | 1.26 ± 1.32 |
| Range | 0.47 – 3.33 | 0.55 – 12.0 | 0.75 – 1.57 | 0.47 – 12.0 |

mal, on the condition that electrocardiographic, fluoroscopic, and thorough clinical examination did not reveal any cardiac abnormalities.

The ratio of the P/P-R segment, also called the Macruz index, was calculated in every case in each of the three groups of P waves and its significance was evaluated.

A total of 395 records was examined; no distinction was made between records from males and those from females. Basic measurements were taken in the groups of rounded, peaked, and notched P waves. Correlation between the shape of the P wave and length of the P-R interval was then studied in groups, with the P-R interval increasing by 0.02 second from 0.11 to 0.24 second. Each group contained 30 observations. Correlation between age of the subjects and shape of the P wave was also studied in separate age-groups, from under 10 years of age up to 80 years, with a 10-year increase for each group. The incidence of differently shaped P waves is expressed in percentages.

## Results

Table I reproduces the measurements in each of the three groups of P waves. Comparison of the measurements in the groups with differently shaped P waves disclosed significant differences.

*Rounded P waves.* These showed the greatest incidence (56.2 per cent); the longest P-wave duration was 0.101 ± 0.014 second, the longest P-R interval was 0.202 ± 0.021 second, and the longest P-R segment was 0.093 ± 0.028 second.

*Peaked P waves.* These had an incidence of 38.8 per cent. The length of the duration of the P wave was the shortest, 0.086 ± 0.013 second, and so were the duration of the P-R interval, 0.134 ± 0.023 second, and that of the P-R segment, 0.048 ± 0.019 second.

*Notched P waves.* These were observed less frequently (5 per cent). The duration of the P wave was 0.103 ± 0.011 second, the P-R interval was 0.192 ± 0.025 second, and the P-R segment measured 0.089 ± 0.026 second in length; all figures were very similar to those found in the group of rounded P waves.

*Correlation between the shape of the P wave and the length of the P-R interval (Table II).* The incidence of peaked P waves had a negative, and that of the rounded P waves a positive, correlation with the length of the P-R interval. Notched P waves were observed in the zones of the longest P-R interval (0.15 to 0.24 second) with almost equal frequency (6 per cent).

*Correlation between age and shape of the P wave (Table III).* The incidence of peaked P waves decreased and that of rounded P waves increased with advancing age. Notched P waves were observed in the middle and advanced years of life with almost equal frequency.

*Table* II. *Incidence of differently shaped P waves at different lengths of the P-R interval*

| *P-R interval* (*sec.*) | *Incidence of P wave* | | |
|---|---|---|---|
| | *Peaked* (%) | *Rounded* (%) | *Notched* (%) |
| 0.11-0.12 | 98.5 | 1.5 | |
| 0.13-0.14 | 90.0 | 10.0 | |
| 0.15-0.16 | 48.3 | 45.0 | 6.7 |
| 0.17-0.18 | 15.0 | 75.0 | 10.0 |
| 0.19-0.20 | 3.3 | 90.7 | 6.0 |
| 0.21-0.22 | | 94.0 | 6.0 |
| 0.23-0.24 | | 94.0 | 6.0 |

*Table* III. *Correlation between differently shaped P waves and age*

| *Age* (*yr.*) | *Incidence of P wave* | | |
|---|---|---|---|
| | *Peaked* (%) | *Rounded* (%) | *Notched* (%) |
| 0-10 | 100.0 | | |
| 11-20 | 77.0 | 23.0 | |
| 21-30 | 57.0 | 40.0 | 3.0 |
| 31-40 | 42.0 | 49.5 | 8.5 |
| 41-50 | 39.0 | 57.5 | 3.5 |
| 51-60 | 26.0 | 68.0 | 6.0 |
| 61-70 | 26.0 | 65.5 | 8.0 |
| 71-80 | 20.0 | 73.0 | 7.0 |

## Discussion

The normal spread of impulses is associated with a series of bioelectric currents which, when algebraically summated, give rise to smooth, rounded P waves. When, as often happens, summation is not so perfect, the P wave becomes peaked or shows tiny notches (Wiggers[4]). The influence of autonomic nerves on the shape of the P wave was demonstrated experimentally by Rothberger and Winterberg[5]—increase of the vagal tone produced rounding and decreased height; increase of the sympathetic tone, a peaking and increased height of the P wave. The influence of electrolytes on the shape of the P wave has also been established both experimentally and clinically. Weller and associates,[6] and Surawicz and Lepeschkin[7] have observed tall, peaked P waves in cases of hypopotassemia, whereas in cases of hyperpotassemia there was a decrease in the height of the P wave, even to the extent of suppression. Factors which control the morphogenesis of the P wave are multiple and still imperfectly understood.

The two basic morphologic variations of the P wave are peaked and rounded shapes. P waves of these two configurations differ from each other not only in their shape but also in their definite sizes and in their correlations.

Peaked P waves are generally taller and of shorter duration than rounded P waves. The average height of peaked P waves in Lead II measured 1.45 ± 0.52 mm., and the average duration was 0.086 ± 0.013 second. Rounded P waves were an average height of 1.16 ± 0.37 mm. (−20 per cent) and had an average duration of 0.108 ± 0.14 second (+27 per cent). These differences are not incidental but *basic*, and correspond to a different structure. As far as the duration is concerned, the standard error of the mean (S.E.M.) duration of the peaked P wave, expressed by the formula $\sqrt{\frac{\Sigma\ (\delta^2)}{n\ (n-1)}}$, measured ± 0.001 second, so that the limit of variation caused by simple chance equals 3 S.E.M., i.e., ± 0.003 second. The difference between the average durations of peaked and rounded P waves amounted to 0.022 second, equaling 22 standard errors, and is, therefore, statistically significant. Furthermore, the average length of the P-R interval in cases of peaked P waves measured 0.134 second, whereas that in cases of rounded P waves amounted to 0.202 second, i.e., 50 per cent longer. The P-R segment was noticeably shorter in cases of peaked P waves, averaging 0.048 second, whereas that in cases of rounded P waves exhibited an average length of 0.930 second, indicating an increase of 91 per cent.

Peaked and rounded P waves had a negative correlation with age and with the length of the P-R interval. Peaked P waves are more common in youth, and decrease in frequency with advancing age. Rounded P waves are infrequent in youth and more common in the aged.

Again, peaked P waves are more frequently associated with a short P-R interval, and rounded P waves, with a prolonged P-R interval. Thus, the incidence of peaked P waves in the group with the shortest P-R interval, from 0.11 to 0.12 second, was 98.5 per cent, and that of rounded P waves was 1.5 per cent. This proportion was inverted in the group with the longest P-R interval, from 0.23 to 0.24 second, in which peaked P waves were absent and rounded P waves showed an incidence of 94.0 per cent.

Notched P waves in their morphologic structure and behavior resembled the rounded P waves.

Morphologically, the normal P-R interval, representing the duration of the passage of the excitation wave from the sinus node to the ventricular muscle, is composed of two sections: the P wave that represents the spread of activation through the auricular muscle, and the P-R segment that indicates the delay of stimulus caused by the auriculoventricular node. The functional state of the conducting system depends on various factors, e.g., blood supply, autonomic nervous control (especially intensity of the vagal tone), adrenocortical hormones (Lown et al.[8]), etc.

There is some difference of opinion with regard to the upper limit of the normal P-R interval. Most authorities consider it to be as long as 0.20 second (Wilson,[9] White,[10] Goldberger,[11] Luisada,[12] Scherf and Boyd[13]). Averill and Lamb[14] define any A-V conduction over 0.21 second as first-degree A-V block. However, it is generally accepted that the normal P-R interval may occasionally be longer than 0.20 second. Ferguson and O'Connel[15] found in over 1.0 per cent of the electrocardiograms of 1,812 healthy young men a P-R interval which was longer than 0.20 second; and Hall, Stewart and Manning[16] made the same finding in nearly 2 per cent of 2,000 apparently healthy young men. In the electrocardiograms of 1,000 aviators, Graybiel and associates[3] observed P-R intervals which lasted 0.21 second in 4 cases, 0.22 second in 8 cases, and 0.24, 0.25, 0.26, and 0.28 second in 1 case each. Therefore, our upper limit of 0.24 second for the normal P-R interval can be considered physiologic.

As already stated, the length of the P-R interval is correlated with the shape of the P wave—peaked P waves prevail with short P-R intervals, and rounded and notched P waves with prolonged P-R intervals. This correlation can be explained satisfactorily by invoking the influence of autonomic nervous tone on the heart muscle.

Macruz and associates,[17] elaborating their pathophysiologic findings, correlated the duration of the P wave with the corresponding P-R segment as an index of atrial enlargement. They found that the ratio of P/P-R segment varies in normal subjects from 1.0 to 1.6. We have investigated this particular problem, using the present observations, and found that the total average (1.26 ± 1.32), as much as the averages of the differently shaped P waves (rounded 1.17 ± 0.30, notched 1.16 ± 0.47, peaked 1.76 ± 1.69), agreed with the above-stated range of the mean ratio. However, in this group of normal subjects the ranges observed were so wide (0.47 to 12.0) that clinical use of the ratio for the electrocardiographic detection of atrial enlargement was negligible. Pipberger and Tanenbaum[18] also found, in 133 healthy subjects, that the ranges of this ratio were equally wide (0.97 to 10.17). On the other hand, Soloff and Zatuchni,[19] determining the volume of the atria by biplane stereoscopic venous angiography, could not find any significant correlation between the ratio of P/P-R segment and atrial enlargement. Therefore, it appears that the clinical value of the ratio of Macruz is highly questionable.

## Summary

1. P waves may exhibit different shapes, sizes, and, also, correlations.

2. Peaked P waves are, on an average, taller and of shorter duration than rounded P waves. They are associated with a short P-R interval and are found in younger age-groups. Rounded P waves are found with greater frequency in the older age-groups and are associated with a prolonged P-R interval.

3. Notched P waves behave as rounded atrial waves.

4. Correlations between the shape of the P wave and the length of the P-R

interval are explained by the intervention of autonomic nerves, especially by differences in the vagal tone.

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# Arterial embolization in relation to mitral valvuloplasty

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Peripheral arterial embolization is a potential hazard throughout the life span of patients with mitral valvular disease, particularly those who are in atrial fibrillation. The knowledge of this hazard, with the possibility of death or permanent paralysis occurring at any time, is a sword of Damocles over the heads of patients with rheumatic heart disease and especially those who have already had one embolus. A number of different forms of therapy have been advocated to prevent such emboli, which ordinarily arise from thrombi in the left atria. Two of these measures have been the conversion of the atrial fibrillation to sinus rhythm, and the long-term administration of anticoagulant agents to patients in atrial fibrillation who have had one or more emboli. The first method is not widely used because of the potential danger of dislodging an embolus at the time of conversion, the hazards inherent in quinidine therapy, and the difficulty in restoring normal rhythm in these patients, for the majority will again revert to atrial fibrillation. The method of long-term administration of anticoagulant drugs obviously has inherent difficulties in the regulation of this condition, and there is a risk of bleeding. However, there is evidence which suggests that there was a decrease in the occurrence of emboli in patients who were successfully carried on these drugs.[1]

A third method of prophylaxis is by cardiac operation. Originally, amputation of the left atrial appendage was advocated[2] to diminish the area in which the formation of a thrombus might take place, but, since mitral valvuloplasty was shown to be a reasonably safe and effective procedure in patients with mitral stenosis, and since less than half of the atrial clots are confined to the appendix, simple appendectomy has been largely abandoned in favor of mitral valvuloplasty, which includes varying degrees of amputation of the auricular appendage. We have presented evidence[3] that such operation for mitral stenosis does indeed exert a protective effect against the formation of emboli later on. Others with extensive experience in mitral valve operation have reported similar beneficial results.[4-9,22-24] Recently, however, two papers[10,11] were presented before the American Heart Association which cast some doubt on the usefulness of mitral valve operations in preventing the formation of emboli, and emphasized the hazard of operative embolization. The purpose of this article is to extend our previous report by presenting in greater detail the results in a larger number of patients followed up for a longer period of time.

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No attempt will be made to discuss all of the aspects of the formation of arterial emboli in patients with rheumatic heart disease. A recent article by Askey and Bernstein[12] summarized the current thinking in this regard and much of the relevant literature. Reference is made to this article and to Askey's monograph, *Systemic Arterial Embolization,*[1] for discussion of aspects of the problem other than those related to mitral valvuloplasty.

The present statistics are based on a follow-up study of the first 1,500 patients with predominant mitral stenosis who were operated upon by Harken and his associates by means of closed valvuloplasty. Follow-up statistics on the first 1,000 patients of this group have already been reported,[3] as has our classification,[13] which roughly corresponds to that of the American Heart Association. No patient was without symptoms (Group I). There were 30 patients in Group II, those with mild and static symptoms. The few patients who were operated upon because of previous emboli and who otherwise had no symptoms were placed in this group. The 1,123 patients in Group III were those with progressive symptoms, mostly pulmonary. There were 347 patients in Group IV, which was composed of cardiac invalids.

## Operative embolization

For the purpose of this discussion, *operative embolization* is defined as a peripheral embolus which occurred at the time of the mitral valvuloplasty or while the patient was still hospitalized postoperatively. Virtually all of the 89 embolic phenomena occurred in the operating room. Only 13 occurred more than 12 hours after operation: 7 within 72 hours, and 6 from 4 to 21 days after operation. Of these 13 emboli, 7 occurred in the patients of Group III, and 4 in patients who were in normal rhythm.

The incidence of operative emboli is indicated in Table I. As we reported previously,[14] embolization occurred in the first 100 patients more frequently than in patients who were operated upon subsequently, but there has been no significant trend since that point. Emboli were formed more often in the patients of Group IV than in those in Groups II and III, and occurred twice as frequently in the patients of Groups II and III who were fibrillating as in those in normal rhythm. This difference with rhythm was not apparent in the patients of Group IV, the vast majority of whom were in atrial fibrillation. Patients who had had emboli preoperatively had a greater incidence of operative embolization than did those who had never had such documented attacks. All of these differences are statistically significant ($p < 0.01$). Eleven of the 49 emboli in the patients of Group III were fatal (23 per cent), and 27 of the 40 in the patients of Group IV (67 per cent). Operative embolization accounted for about a third of the deaths during operation in both Groups III and IV. The over-all operative mortality in the patients of Groups II and III was 2.7 per cent, and in the patients of Group IV it was 22.8 per cent. This includes the much higher mortality in the operations carried out early in the series, which we have commented on.[3,14] Excluding deaths related to operative embolization, the death rates were reduced to 1.7 and 15.0 per cent, respectively. The experience of others is similar to ours, and has been analyzed by Askey and Bernstein.[12]

Although most emboli came from a dislodged thrombus in the atrium or atrial appendage, another source was fragments which were splintered off at the time of fracture of a calcified valve. It was impossible to obtain accurate figures on the incidence of this latter hazard because patients with heavily calcified valves frequently were severely ill, in atrial fibrillation, and had mural thrombi in the atrium.

The prevention of thrombi becoming emboli has been accomplished largely by the avoidance of areas in which thrombi were present, by minimal atrial manipulation, by freely flushing the atrium at the time of the incision of this structure (before the finger is inserted), and by recognizing and carefully sucking out the thrombi from the atrial appendage before the atrial clamp is released. At one time it was thought that occlusion of the head vessels, as advocated by Bailey and associates,[15] might diminish the likelihood of embolization, and this was carried out in many of the first 200 or 300 patients.

It did not, however, materially diminish the incidence of embolization, and the cerebral anoxia due to the occlusion of head vessels may have had a deleterious effect. Therefore, this was abandoned except in patients who had heavily calcified valves, and in whom fracture had to be carried out through the calcified area.

Other authors have suggested additional methods whereby the risk of embolization may be minimized. Bailey and Morse[16] have argued that an approach through the right side diminished the likelihood of embolization, because the entry to the left atrium is not through the left atrial appendage, which is one of the most frequent sites of the formation of thrombi. In this connection, however, it is well to point out that, since this approach does avoid the left atrial appendage, it eliminates at the same time an atrial appendectomy which may be one of the important factors in the prevention of subsequent emboli. Storm[17,18] has suggested that operation while the patient is under anticoagulant therapy is worth while and diminishes the hazards of embolization, and Goodwin[19] has suggestive evidence which confirms this. Although Storm's figures did not indicate an increased hazard from bleeding, it is our belief that the safety of this procedure has not been established.

## Preoperative embolization

Two hundred sixty patients of the group of 1,500 had had one or more well-documented attacks of arterial embolization sometime prior to operation; the time varied from 1 day to many years. It was impossible to determine with accuracy how many of these patients were in atrial fibrillation at the time of the embolization, or when the fibrillation developed. At the time of operation, 212 patients showed atrial fibrillation and 48 were in normal rhythm.

Patients who had had one or more emboli within 8 weeks prior to the time of operation had twice as many operative emboli as did those in whom embolization occurred earlier (Table II). If the patients of Group III and Group IV are considered separately, the results are not statistically significant; but when the two groups are combined, the results are significant by the chi-square test to the 5 per cent level. Although many of these patients were operated upon as semi-emergency cases because of showers of emboli (23 of the 96 in this group), the incidence of operative emboli was the same as in those who had had a single embolus. The differences cannot be explained on the basis of any differing complexion of the patient population in regard to group or rhythm. Within the 8-week period there was no trend in regard to the frequency of embolization. In patients operated upon more than 8 weeks after an embolus, the time duration was also of no demonstrable significance (Table III).

## Atrial thrombosis

Obviously, the likelihood of embolization is related to the occurrence of atrial thrombosis. Whether or not an atrial thrombosis was noted by the surgeon at the time of valvuloplasty is reported in 1,246 of the 1,500 cases. It will be seen from Table IV that the incidence of such thrombi varied according to group and rhythm in the same manner as did the incidence of operative embolization, namely, it was higher in the patients of Group IV than in those of Group III, and in the fibrillating patients of Group III when compared with those who had normal rhythm. It is of interest that thrombi were noted as frequently in patients without a history of preoperative emboli as in those who had had one or more embolization.

Although a fresh, friable thrombus is more likely to be detached to form an embolus than is an old one, we did not attempt to distinguish between the two in this study. Since the incidence of thrombi was not significantly different in the group operated upon within 8 weeks and the group operated upon more than 8 weeks after an embolus, there probably is a greater frequency of fresh thrombi in this group.

## Late postoperative emboli

Late postoperative emboli are defined as those occurring after the patient had left the hospital after mitral valvuloplasty. One thousand three hundred ninety patients survived operation, and these have been followed up for periods up to 11 years

*Table I. Incidence of operative emboli in relation to classification of patients, rhythm, and the occurrence of preoperative embolization*

| | *Number of patients* | *Number of operative emboli* | *Per cent of operative emboli* |
|---|---|---|---|
| Groups II and III | | | |
| Without preoperative emboli | | | |
| Normal sinus rhythm | 602 | 15 | 3 |
| Atrial fibrillation | 356 | 17 | 5 |
| With preoperative emboli | | | |
| Normal sinus rhythm | 43 | 4 | 10 |
| Atrial fibrillation | 153 | 13 | 9 |
| Total | | | |
| Normal sinus rhythm | 645 | 19 (3)* | 3 |
| Atrial fibrillation | 509 | 30 (8)* | 6 |
| Combined | 1,154 | 49 | 4 |
| Group IV | | | |
| Without preoperative emboli | | | |
| Normal sinus rhythm | 75 | 7 | 9 |
| Atrial fibrillation | 207 | 18 | 9 |
| With preoperative emboli | | | |
| Normal sinus rhythm | 5 | 1 | 20 |
| Atrial fibrillation | 59 | 14 | 24 |
| Total | | | |
| Normal sinus rhythm | 80 | 8 (3)* | 10 |
| Atrial fibrillation | 266 | 32 (24)* | 12 |
| Combined | 346 | 40 | 12 |

*Fatal emboli.

*Table II. Incidence of operative embolization in patients who had emboli within 8 weeks before operation versus those who had earlier emboli*

| *Group* | *Preoperative emboli* | | | | | |
|---|---|---|---|---|---|---|
| | *Within 8 weeks before operation* | | | *More than 8 weeks before operation* | | |
| | *Number of patients* | *Number of operative emboli* | *Per cent of operative emboli* | *Number of patients* | *Number of operative emboli* | *Per cent of operative emboli* |
| II and III | 77 | 10 | 13 | 119 | 7 | 6 |
| IV | 19 | 7 | 37 | 45 | 8 | 18 |
| Both* | 96 | 17 | 18 | 164 | 15 | 9 |

*p value = 0.05.

by annual questionnaires, by personal examination in many instances, and by additional information from the patient, his doctor, or his hospital, as described elsewhere.[3] Thirty-eight patients have had definite peripheral emboli which occurred after they left the hospital after the mitral valvuloplasty. Three of these patients had two emboli. There were 25 cerebral vascular accidents and 16 emboli to major

arteries elsewhere in the body. Seven of the episodes of embolism were fatal. Twenty-seven of the patients were classified in Group III prior to their operation, and 11 in Group IV. This proportion between the two groups is similar to that of the entire group of 1,500. In 12 patients who were in normal rhythm at the time of operation, atrial fibrillation developed later. Four patients were in normal sinus rhythm at the time of operation, and we have no definite knowledge that their rhythm changed subsequently. Of this group of 38 patients, 6 had had preoperative emboli, and 5 had had operative emboli. There is no evidence that postoperative embolization developed in patients who were doing poorly or had undergone an inadequate valvuloplasty, because almost all of the patients had what was considered to be an "adequate" operation at the time it was performed. At their annual follow-up examination immediately prior to the occurrence of the peripheral embolus, 23 of the 38 patients had been classified as moderately to markedly improved in their over-all cardiac status. Three had been classified as slightly improved, and 3 as unchanged as the result of the operation. Eight developed their peripheral emboli within the first year, before the first annual follow-up examination, and we do not have accurate reports of their cardiac status at this time. In one patient who had been operated upon more than 1 year before there was

*Table* III. *Incidence of operative emboli in patients with preoperative emboli in relation to time of occurrence*

| *Time of emboli before operation* | *Groups II and III* | | | *Group IV* | | |
|---|---|---|---|---|---|---|
| | *Number of patients* | *Number of operative emboli* | *Per cent of operative emboli* | *Number of patients* | *Number of operative emboli* | *Per cent of operative emboli* |
| 0–8 wk. | 77 | 10 | 13 | 19 | 7 | 37 |
| 9–16 wk. | 17 | 1 | 6 | 3 | 0 | 0 |
| 17–25 wk. | 18 | 1 | 6 | 2 | 0 | 0 |
| 26–52 wk. | 18 | 2 | 11 | 5 | 1 | 20 |
| 1–2 yr. | 25 | 1 | 4 | 15 | 3 | 20 |
| 2 yr. or more | 41 | 2 | 5 | 20 | 4 | 20 |
| Total | 196 | 17 | 9 | 64 | 15 | 23 |

*Table* IV. *Incidence of atrial thrombosis in relation to severity of disease, rhythm, and the occurrence of preoperative emboli*

| *Number of patients with preoperative emboli* | *Groups II and III* | | | | *Group IV* | | | |
|---|---|---|---|---|---|---|---|---|
| | *Normal rhythm* | | *Atrial fibrillation* | | *Normal rhythm* | | *Atrial fibrillation* | |
| | *Total number* | *Per cent with thrombi* | *Total number* | *Per cent with thrombi* | *Total number* | *Per cent with thrombi* | *Total number* | *Per cent with thrombi* |
| Absent | 471 | 4 | 295 | 52 | 55 | 16 | 178 | 73 |
| Present | 42 | 10 | 142 | 51 | 5 | 80 | 58 | 74 |
| (Preoperative emboli within 8 wk.) | (17) | (6) | (52) | (36) | (2) | (100) | (13) | (61) |

no follow-up examination. As a whole, the improvement status of these patients was about the same as that for the entire group of 1,500 patients.

The emboli occurred from 1 month to 7 years after the operation, and there was a fairly constant scatter throughout this period. Twenty-two incidences of embolic episodes occurred between 1 and 4 years postoperatively, with the maximum between 2 and 3 years, when there were 12. Six years is the mean follow-up examination period for this group of 1,390 survivors. Obviously, all 1,390 patients have not been followed up from operation to the present time. There have been 160 late deaths, 7 in which late peripheral embolization played a role. One hundred twenty-seven patients had had a second cardiac operation because of recurrent symptoms. Thirty have been lost from the series after varying periods of follow-up. Sixty-three are delinquent in their follow-up examination for periods which vary from a few months to a year. The other 992 have been followed up to the current anniversary of their operation. It is obvious that those who died, those who were reoperated upon, and those who are delinquent were followed up for varying periods of time after operation. It is difficult, therefore, to estimate the follow-up period in patient-years, but it lies somewhere between the 992 patients who are currently being followed up and the total 1,390. Therefore, the incidence of embolization in the group as a whole would fall somewhere between 0.46 and 0.64 per cent per patient per year.

All patients who suffered from cerebral vascular accidents were classified as having had them because of cerebral emboli. Inasmuch as the average age of the patients who had late peripheral embolization was 45 years at the time of operation, it is possible that some of these patients had cerebral vascular accidents as a result of thrombosis or hemorrhage. In addition, in the cases under discussion, 2 patients were strongly suspected of having subacute bacterial endocarditis at the time at which the embolization took place, and a third patient had a fatal cerebral embolus 2 days after catheterization of the left side of the heart.

## Anticoagulant therapy

Fifty-eight of the 96 patients who had had preoperative emboli within 8 weeks of operation had been on anticoagulant therapy. The type and extent of such therapy varied greatly and in many cases was clearly inadequate. No beneficial effect of such treatment was demonstrable in preventing operative emboli. There was also no clear evidence that atrial thrombosis was diminished in patients who received anticoagulant drugs, although the suggestively lower incidence of atrial thrombosis in patients who had had a preoperative embolus within 8 weeks of operation, as compared to others (Table IV), may reflect the greater use of such drugs in those patients.

The results of anticoagulant therapy are not presented in detail, since a fair evaluation of such prophylactic therapy cannot be made from our data. Except in very rare instances, anticoagulant drugs were not given after operation, either early or late.

## Discussion

The purpose of this study has been to define the conditions under which peripheral embolization takes place in patients with mitral valvular disease in relation to mitral valvuloplasty. The incidence of clear-cut preoperative embolization in this group was 17 per cent; other authors have reported a somewhat greater incidence. The difference may be due to the severity of our criteria of definition, for we included only patients who had unquestioned emboli.

Operative embolization remains an inherent risk of the procedure and is a major factor in the operative mortality. It is clear that there are certain conditions which modify the likelihood of embolization at the time of operation, quite aside from any special techniques that may be aimed at avoiding them. The presence of atrial fibrillation, increasing severity of heart disease, and the occurrence of preoperative embolization all heighten the risk. This has been shown by others as well as ourselves. Undoubtedly, the existence of heavy calcification of the mitral valve also increases the risk of calcific emboli, but this has not been analyzed in

the current study. All of the conditions that increase the risk of operative embolization also contribute to the severity of heart disease as a whole and are, in themselves, indications for cardiac operation. It is impossible, therefore, to define the risk to a patient of a possible embolus at the time of operation except in terms of the general condition of that patient. In the abstract of a presentation by Taber and Lam,[11] for instance, there is no mention of the severity of disability or of the classification of the patients. It is suggested in this report that fibrillation itself is a bad thing to have in relation to embolization. Whereas this is undoubtedly true, it is equally true that most patients who are seriously disabled are also in atrial fibrillation. Other factors leading to the severity of their heart disease must be considered and defined.

Our findings suggest that embolization within 8 weeks before operation carries a higher risk of operative embolism than if such preoperative embolus had occurred earlier, presumably because it is more likely that a friable clot is present in the atrium.

Our present findings confirm our previous reports in respect to the protective value of mitral valve operation against future embolization. With the passage of time and with the experience of an increasing number of patients, the annual incidence of such embolization has not tended to increase. It has not been our practice to attempt to convert patients in chronic fibrillation to sinus rhythm except in rare instances. In our earlier follow-up study[3] it was shown that the incidence of fibrillation in patients a number of years later was the same as at the time of operation; the few patients who had reverted to normal rhythm about balanced the number who developed atrial fibrillation postoperatively. Since two of the factors that are undoubtedly responsible for protection against late peripheral embolization are the reduction of stasis in the left atrium by adequate valvuloplasty and amputation of the left atrial appendage, it is reasonable to believe that patients in whom these two measures have not been accomplished would be more likely to develop peripheral embolization. In our experience we could not demonstrate any relationship between an inadequate valvuloplasty and the occurrence of late emboli. It must be recognized, however, that an "adequate" operation by 1952 standards may be far from adequate when judged by current techniques. Virtually complete atrial appendectomy was carried out routinely later on in the series.

Almost all of the patients under discussion had symptoms of cardiac disability, and one of the prime indications for operation was the evidence of high-grade mitral stenosis which produced symptoms which could be, and usually were, relieved by such operation. Therefore, any protective effect against embolization was, in many of these patients, considered to be an added dividend rather than the prime indication for operation. There was a handful of patients in whom the sole indication for operation was the existence of previous emboli. The decision in favor of operation is easy if there is a clear-cut reason for mitral valvuloplasty on the basis of cardiac disability alone. We have discussed such indications elsewhere. It is important to appreciate, however, that patients without severe mitral stenosis who fibrillate and who may develop emboli may represent a somewhat different type of patient than the usual one who fibrillates late in the course of the disease. Although significant mitral stenosis may exist without symptoms,[21] it is nevertheless a fact that in many of the patients in this group the mitral stenosis is mild and there is little stasis in the left atrium. In these patients, other factors may be present which result in the development of fibrillation and in a tendency to the formation of thrombi, such as a greater than usual degree of atrial endocarditis and myocarditis with scarring or some peculiarity in their clotting mechanism. Hence, one cannot with complete assurance translate all statistics that have been reported on the protective effect of mitral valvuloplasty against embolization to patients without symptoms but with lesser degrees of mitral stenosis. This is particularly true of patients in the older age group who often develop symptoms and have fibrillation precipitated by degenerative changes

of atherosclerosis superimposed on a moderate amount of rheumatic heart disease.

The critical question is: Should mitral valvuloplasty be recommended in all patients with mitral valvular disease who have had an embolus, or, indeed, in all patients with mitral valvular disease who are fibrillating? Or, can one define limiting criteria which can be applied in the selection of patients who are suitable for operation?

Patients with mitral stenosis who are most likely to develop emboli are those who are fibrillating (75 or more per cent) and over 40 years of age. The embolus may occur promptly with the onset of fibrillation or be delayed for many years.[20] The probability of a patient developing an embolus is not known exactly. Bannister[25] found that 22 of 105 patients with moderate mitral stenosis followed up for an average period of 4½ years developed peripheral emboli. In Olesen's series[26] of 271 patients with mitral stenosis, 75 developed peripheral emboli (27 per cent). Most of these patients were over 45 years of age, were in a late stage of their disease, and 85 per cent were fibrillating. Twenty-three per cent of Wilson and Greenwood's series[27] of patients with mitral valvular disease developed emboli.

Askey[1] has estimated that 25 to 30 per cent of the patients with mitral valvular disease die as the result of emboli. These emboli occur more frequently in patients with cardiac disability and failure, but there is a substantial percentage in whom this disaster is the first important cardiac symptom.

The likelihood that a patient who has survived an embolus will have a second one is excellent. Daley and associates[20] found that about a third of their group of 194 patients who had peripheral emboli developed one or more recurrences, and about a third of the recurrences were within 1 month. They found that 12 per cent died as the result of their first embolus, and in an additional 28 per cent, death resulted from the recurrences. In our series of 260 patients with preoperative emboli there were 16 (6 per cent) who developed a second embolus within 8 weeks. Our series may well have been slanted in favor of patients with multiple emboli within a short period, because such patients would have been more likely to be referred for operation.

Although the risk of operative embolization is increased in patients who are fibrillating, who have had previous emboli, and who have more advanced disease, the risk of spontaneous embolization is also increased in these same patients if they are not operated upon. Similarly, the increased risk of operation within 8 weeks of an embolus is about balanced by the possibility that the patient will have recurrent spontaneous emboli.

When all considerations are taken into account, there is a strong indication for mitral valve operation in all patients who have had a peripheral embolus, even without significant symptoms of cardiac disability, as a protection against future emboli. Although the argument for prompt operation is, in general, at least as strong as that in favor of delaying the operation for several weeks, each patient must be considered on his individual merits. Consideration must be given to such factors as the general condition of the patient, the presence of treatable heart failure, and the risk of aggravating brain damage if operation is carried out too soon after a cerebral embolus, as well as other factors.

At the present time we do not have evidence indicating that patients in fibrillation but without symptoms who have not suffered an embolus should routinely undergo valvuloplasty. Such patients should receive careful study and close medical follow-up, and, in many of these, added indications pointing toward surgical intervention will develop soon.

Most of our patients did not have adequate treatment with anticoagulant drugs. Although an anticoagulant drug, given in a "routine" manner for a short period, may not greatly influence the likelihood of an operative embolus, it is possible that it will diminish the possibility of repeated emboli occurring in the period before operation. Indeed the reported studies[1] on the prolonged use of anticoagulant drugs would suggest that this is so; in the light of our present knowledge it would seem advisable to administer them from the time of an embolus until mitral valvuloplasty is carried out. Whether or not

they should be continued during the operative period is still a moot point on which this study throws no light.

Since the incidence of emboli occurring after the immediate surgical period is so low, it is our opinion that the risk of routine administration of anticoagulant agents at this time is greater than the possible benefit. Very few of the patients were on long-term anticoagulant therapy after the operation, and we have not recommended this routinely because of the low incidence of late embolization.

## Summary

The present study is based on our experience of peripheral arterial embolization in 1,500 consecutive patients with predominant mitral stenosis who underwent mitral valvuloplasty. The purpose of this study has been to define the conditions under which such embolization takes place. It has been shown that the presence of atrial fibrillation, increasing severity of heart disease, and the occurrence of preoperative embolization all increase the risk of operative embolization, which remains an inherent risk of the procedure and is a major factor in deaths from operation.

Our findings suggest that an embolus within 8 weeks of operation carries a higher risk of operative embolization than does a preoperative embolus occurring earlier.

Our present findings confirm our previous reports with respect to the protective value of mitral valve operation against future embolization. Late postoperative emboli have occurred in 38 patients of the entire group followed up for a mean period of 6 years, an incidence of 0.46 to 0.64 per cent per patient-year.

Our figures show no beneficial results from preoperative anticoagulant therapy as given—for most it was given for a short period and stopped several days prior to operation—but shed no light on anticoagulant treatment given intensively for longer periods or through the period of operation. The low incidence of embolization after the immediate operative period would suggest that the routine administration of anticoagulant agents is unnecessary in the postoperative period, either early or late.

The formation of peripheral emboli is an indication for mitral valvuloplasty in patients with mitral stenosis, even without symptoms. In certain patients the increased risk of operative embolization is about balanced by the increased hazard of recurrent spontaneous embolization.

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# Observations with the Frank system of vectorcardiography in left ventricular hypertrophy

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The accuracy of the electrocardiographic diagnosis of left ventricular hypertrophy (LVH) is an unsettled issue. Some investigators have concluded that the electrocardiogram is the most reliable clinical indicator of LVH available,[1] whereas others advise caution in the use of any current electrocardiographic standards for LVH.[2]

Improvement in the dependability of electrocardiographic methods would be welcomed, especially when applied to early or mild examples of left ventricular overload. The employment of newer, theoretically more accurate lead systems in an attempt to define LVH more precisely seems warranted.

The present study was performed to obtain spatial vectorcardiographic data with the Frank lead system in patients with LVH, and to compare the results with those from a group of normal subjects studied previously.

## Patients

Patients were chosen for this investigation on a clinical basis. An evident etiology for LVH was present in each case. Physical and radiographic findings confirmed the hemodynamic importance of the diseases included, and supplementary evidence was provided by right or left heart catheterization and surgical observation in several cases.

The electrocardiogram was not employed in the choice of patients, except that undoubted evidence of myocardial infarction excluded patients from study. Similar methods of selection have been employed by others.[3,4]

Forty-six patients met the desired criteria. There were 7 with congenital valvular, subvalvular, or supravalvular aortic stenosis. Open-heart operation was subsequently performed in 6 of these, and a significant systolic pressure gradient across the aortic valve was measured in the seventh. Four other patients with congenital anomalies which caused left ventricular overload are listed in Table I.

There were 22 patients with rheumatic aortic valvular disease. None was believed to have hemodynamically significant mitral valvular disease. The presence of mitral disease had been excluded in clinically uncertain cases by measurements of left heart pressure and/or by angiography. All patients had the characteristic murmurs of aortic stenosis and/or regurgitation, and left ventricular overactivity or enlargement was noted on physical examination in 20. Left ventricular enlargement

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*Table I. Composition by disease and age of the group of 46 patients with left ventricular hypertrophy*

| Type of disease | Number | Age range | Mean age |
|---|---|---|---|
| Congenital | | | |
| Valvular aortic stenosis | 4 | 15–18 | 20 |
| Subaortic stenosis | 2 | 18–22 | |
| Supravalvular aortic stenosis | 1 | 14 | |
| Coarctation of the aorta | 2 | 30–48 | |
| Tricuspid atresia with subclavian–pulmonary artery anastomosis | 1 | 14 | |
| Aortic medionecrosis with aortic regurgitation | 1 | 40 | |
| Rheumatic aortic valvular disease | 22 | 24–64 | 42 |
| Hypertension | 13 | 35–71 | 52 |
| Total | 46 | 14–71 | 40 |

*Table II. Results of analysis of Frank vectorcardiograms in 41 patients with left ventricular hypertrophy*

| | Horizontal | Left sagittal | Frontal |
|---|---|---|---|
| Angle of maximum QRS vector | 318 degrees (256–359) | 13 ± 21.7 degrees | 15 ± 27.9 degrees |
| Angle of half-area QRS vector | 322 ± 17.4 | 24 ± 22.4 | 18 ± 27.0 |
| Magnitude of maximum QRS vector | 3.29 mv. (1.56–8.96) | 2.32 ± 0.96 mv. | 2.95 ± 1.40 mv. |
| Angle of maximum T vector | 99 degrees (315–167) 37 cases* | 167 degrees (48–252) 37 cases* | 124 degrees (357–230) 36 cases* |
| Magnitude of maximum T vector | 0.81 ± 0.41 mv. | 0.60 mv. (0.23–1.18) | 0.63 mv. (0.29–1.75) |
| Maximum QRS vector–T vector angle | 140 degrees (13–210) | 152 degrees (32–227) | 115 degrees (1–212) |
| Half-area QRS vector–T vector angle | 138 degrees (13–198) | 143 degrees (9–207) | 116 degrees (2–202) |
| Direction of inscription | | | |
| Counterclockwise | 33 | 32 | 16 |
| Clockwise | 1 | 0 | 7 |
| Linear or figure-of-eight | 7 | 9 | 18 |
| QRS loop area | 3.28 units (0.32–14.22) | 1.65 units (0.23–7.04) | 1.48 units (0.13–9.14) |
| QRS loop area in 72 normal subjects | 1.40 ± 0.64 units | 0.84 ± 0.53 units | 0.49 units (0.06–1.50)† |

*T loop was isoelectric in the other cases.
†See text for discussion.
Means ± standard deviations are listed for the LVH data which had normal distributions. The results from non-normal distributions are presented as means, with the absolute ranges observed shown in parentheses below them. At the bottom of the Table, measurements of QRS area for normal subjects are presented. Abbreviation: mv. = millivolt.

was demonstrated by radiographs or left ventricular angiography in 21.

Thirteen patients with systemic hypertension are included. All had significant disease, as indicated by diastolic blood pressures above 100 recorded on most of their visits to the outpatient clinics or hospital during a period of over a year.

The ages of the various groups are shown in Table I. Two of the teen-age patients weighed less than 100 pounds, and one of these was the lightest of the entire series (80 pounds).

There have been 7 deaths, and LVH was verified anatomically in all, with heart weights ranging from 540 to 860 grams.

In summary, patients were chosen who had definite clinical evidence of diseases which result in LVH, and electrocardiographic signs thereof were not employed in this selection. To avoid the problem of biventricular hypertrophy, only conditions which result in pure left ventricular overwork were considered, although some patients with long-standing or severe heart failure were included.

## Method of study

Direct spatial vectorcardiograms (VCGs) were obtained with the lead system described by Frank.[5] The fifth intercostal space at the sternum was used as the level for the chest electrodes, and the examination was conducted with the patient seated. The VCGs were photographed in the horizontal, left sagittal, and frontal projections with 35-millimeter film. It was later projected in an enlarging viewbox, and tracings were made on paper for analysis. Standard calibration factors of 1 millivolt were similarly enlarged. The reference frame employed for angular measurements is shown in Fig. 1. The angles and magnitudes of the maximum QRS and T loop vectors were measured, as well as the angle between them. By means of a planimeter, the QRS loop in each projection was divided into equal half-areas by a line through the isoelectric spot, as described by Pipberger.[6] The angle of this QRS half-area vector was noted, and its relationship to the T loop axis was measured.

As an empirical measurement, the total QRS loop area was determined by planimetry in the enlarged tracing of each projection. In order to compare such areas from patient to patient, an arbitrary unit of area was determined and used as follows. The length of the 1-millivolt signal in the enlarged tracings was known. This length was squared. The resulting area actually represented 1 square millivolt and is hereafter referred to as an area unit. The measured QRS loop area (by planimetry) was divided by the area of this unit, to give a result in numbers of area units.

The planar mean QRS vector in each projection was determined in 21 cases in which the scalar component leads X, Y, and Z were recorded. The algebraically determined net positive or negative area enclosed in the QRS complexes in each lead was determined by planimetry. Results were plotted on right-angle coordinates and angles measured for each projection.

Spatial QRS-T angles were calculated for 72 normal subjects previously reported on, and for the subjects with LVH to be described.[7] The half-area QRS vectors and maximum T vectors in the horizontal and frontal planes were used. Helm's trigonometric tables permit easy determination

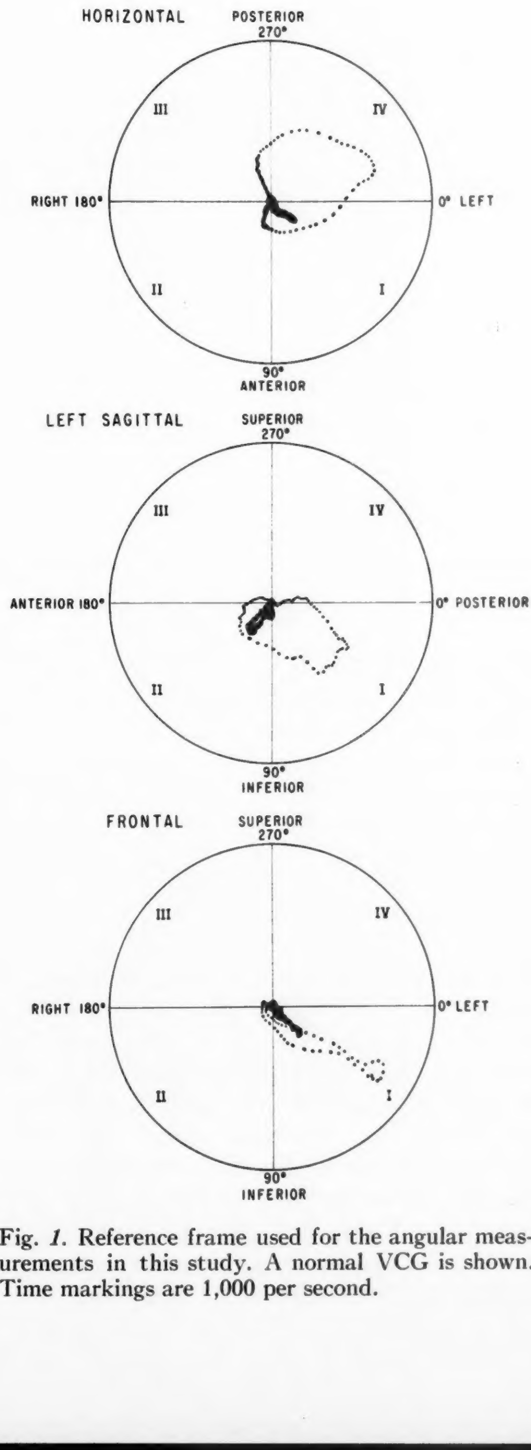


Fig. *1*. Reference frame used for the angular measurements in this study. A normal VCG is shown. Time markings are 1,000 per second.

*Table* III. *Spatial QRS-T angles*

| | Mean | Standard deviation | Range |
|---|---|---|---|
| 72 Normal subjects* (Frank system) | 60° | 19.6° | 10–100° |
| 26 Normal subjects[9] (Frank system) | 51° | 22.0° | ——— |
| 50 Normal subjects[10] (SVEC-III system) | 56° | 18.8° | 20–105° |
| 41 Patients with LVH (this study) | 126° | Not calculated (non-normal distribution) | 35–180° |
| 21 Patients with "left ventricular hypertrophy"[9] (Frank system) | 91° | 27.0° | ——— |
| 15 Patients with "left ventricular strain"[9] (Frank system) | 141° | 21.0° | ——— |

*Spatial QRS-T angles were calculated for a group of normal subjects which has been reported on previously.[7]

*Table* IV. *Probability values from comparison of paired individuals from normal and LVH groups by a nonparametric method**

| | Horizontal | Sagittal | Frontal |
|---|---|---|---|
| Maximum QRS vector magnitude | <0.01 | <0.01 | <0.01 |
| Maximum QRS vector angle | 0.48 | 0.03 | 0.01 |
| Half-area vector angle | 0.03 | <0.01 | <0.01 |
| Maximum T vector magnitude | 0.04 | 0.05 | 0.74 |
| Maximum T vector angle | <0.01 | <0.01 | <0.01 |
| Half-area vector–T angle | <0.01 | <0.01 | <0.01 |

*The Wilcoxon signed rank test was applied to 19 pairs of individuals from the normal and LVH groups who were of the same sex and within 1 year of age of each other. The resulting probability values for most of the measurements indicate significant vectorcardiographic differences between the two groups.

of the spatial QRS-T angle to the nearest 5 degrees, and were employed in this study.[8]

The electronic equipment was of two types. The first part of the study was performed with a Tektronix* RM-32 oscilloscope and two Type 53/54 E differential preamplifiers. Later, Type 122 preamplifiers were used with a Tektronix* 502 oscilloscope, modified for vectorcardiography. This instrument has triggering and wave-brightening circuits which permit photography of the QRS loop alone, without the T loop or glow from the isoelectric spot. The frequency-response adjustments for both instruments were set at 1 kilocycle per second for the high range and 0.06 cycle per second for the low. The beam was interrupted either 400 or 1,000 times per second, and the direction of travel was indicated by the pointed leading edges of the resulting dots.

*Tektronix, Inc., Portland, Ore.

## Results

Five patients who had QRS complex durations of 0.12 second or more were considered to have left bundle branch block (LBBB). The other group of 41 patients is described in detail.

*Left ventricular hypertrophy.* The results from the 41 VCGs are tabulated in Table II. The frequency distribution of many of the parameters did not provide a normal distribution, and standard deviations are presented only in those instances in which a Gaussian distribution was found. The results are compared with the findings in a group of 72 people who were free of heart disease. Details of this study of normal subjects have been reported previously.[7] A given observation in the VCGs

from the LVH group was classified as *abnormal* if it was outside the range of mean ± 2 standard deviations as determined in the normal subjects. A few parameters in the normal subjects had not given Gaussian distributions, and in these cases the absolute ranges previously found were employed as normal limits, with one exception. The measurement of QRS loop area in the frontal projection was below 1.4 units in 70 of 72 controls. (Exceptions were 2.00 and 3.71 units.) The arbitrary upper normal limit was 1.5 units.

QRS LOOP. The most consistent alteration in LVH was the large magnitude of QRS vectors. Thirty-six patients had an abnormally long maximum QRS vector in at least one projection of the loop. The spatial position of the QRS loop did not necessarily present an abnormal maximum vector in all three projections, but it was greater than normal in at least two projections in 31 cases.

Increased QRS magnitude was also evident in the over-all large size of the loops, as indicated by the QRS loop area

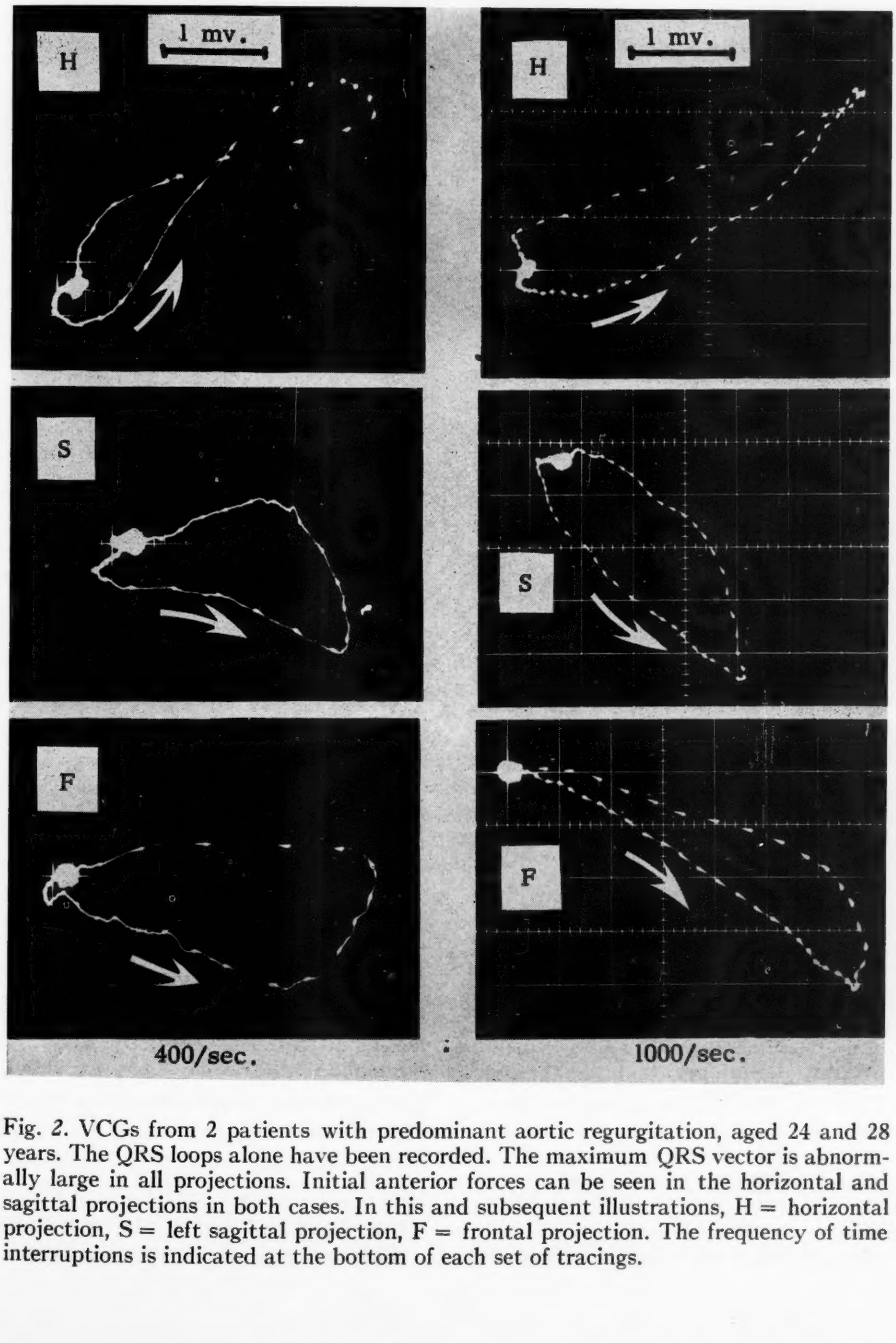


Fig. 2. VCGs from 2 patients with predominant aortic regurgitation, aged 24 and 28 years. The QRS loops alone have been recorded. The maximum QRS vector is abnormally large in all projections. Initial anterior forces can be seen in the horizontal and sagittal projections in both cases. In this and subsequent illustrations, H = horizontal projection, S = left sagittal projection, F = frontal projection. The frequency of time interruptions is indicated at the bottom of each set of tracings.

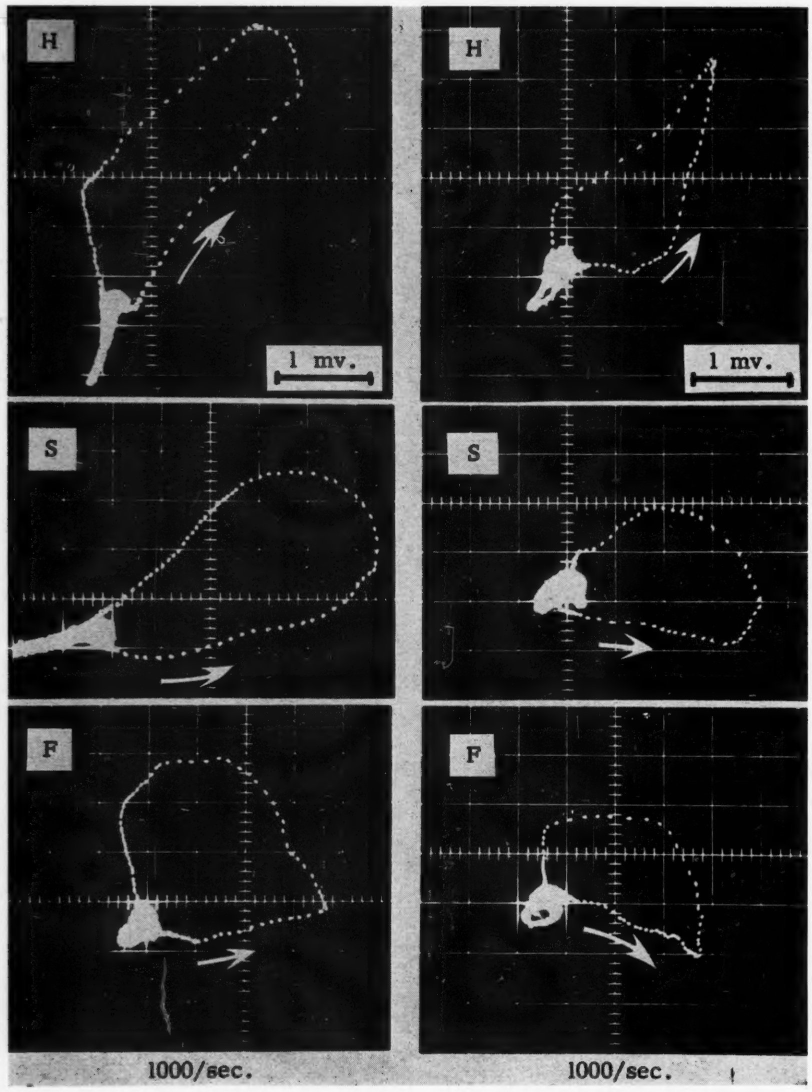


Fig. 3. *Left:* VCG from a 35-year-old man with aortic stenosis. Large maximum QRS vectors are evident in the horizontal and sagittal projections. An abnormally high position of the QRS loop is seen in the frontal projection. Terminal slowing of inscription suggests the presence of an element of ventricular conduction delay. The anterior and rightward location of the T loop is characteristic of cases with the fully developed findings of LVH. *Right:* VCG from an 18-year-old girl with hypertrophic subaortic stenosis. The voltage abnormalities are less marked, although the positional features are similar to those of the case on the left.

measurements. Twenty-nine patients had increases in QRS loop area in at least one projection. Two of the 5 patients who did not have abnormal magnitude of maximum QRS vectors had abnormally large QRS loop areas. Thus, in 3 cases of the entire series the QRS size failed to exceed normal in one or more ways.

The position of the maximum QRS vector was within the normal range in all patients when viewed in the horizontal projection. In approximately one third of the patients there was an abnormally high position of the maximum or half-area QRS vector in the sagittal projection, and in the frontal projection in about one third of the patients. Two of the 3 patients who did not show any abnormality of QRS magnitude demonstrated abnormal elevation of the loop in the sagittal projection. Examples are shown in Figs. 2-5.

From the foregoing it is found that 40

of the 41 patients had at least one abnormality of the position or size of the QRS loop. The sole exception was a hypertensive patient who had no electrocardiographic or vectorcardiographic abnormality.

In all but one case there was discernible initial anterior movement of the QRS loop. The magnitude of this deflection was at times small in comparison to the length of the major loop, but was nonetheless identifiable (see Fig. 6). Initial superiorly directed forces were consistently very small, and often absent. Other qualitative features of the VCGs are listed in Table II.

Occasionally, unusual configuration or position of the QRS loop was found, and examples are shown in Figs. 7 and 8.

T LOOP, S-T VECTORS, AND PLANAR QRS-T ANGLES. T loops were isoelectric or outside the normal ranges of angles in at least one projection in 37 cases. The characteristic location of the major T axis was to the right and anteriorly. More minor shifts of the T axis were present in some patients, and in 4 no abnormality was discerned. There were no examples of isolated T loop or QRS-T angle abnormality without associated changes in the position or magnitude of the QRS loop.

The presence of a rightward, anteriorly directed S-T vector was common in examples with the fully developed picture of LVH.

Abnormalities of the maximum QRS vector–T vector angle were present in two thirds of the group; thus, 13 patients had normal angles. This latter number decreased to 9 if the half-area QRS vector–T angles were considered.

Previous studies by Pipberger[6] showed a dependable similarity between the half-area QRS vector angle and the true mean QRS vector angle, using the SVEC-III system. Comparison of the half-area vectors from one study with the mean planar QRS vectors from another suggested the same consistency when the Frank system was used in normal people.[7] A comparison was made between the half-area QRS and the planar mean QRS vector angles in 21 of the patients in this investigation. In general, the values were very close. The mean differences between the two measurements in these 21 VCGs were: 6.1 degrees in the horizontal, 7.1 degrees in the sagittal, and 4.5 degrees in the frontal projection. One or two larger discrepancies, from 20 to 30 degrees, were found in each projec-

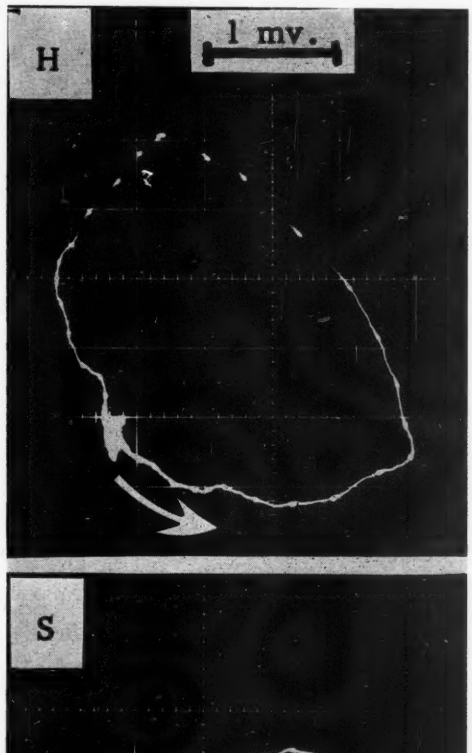


Fig. 4. The QRS loops alone were recorded in this VCG from a 55-year-old man with hypertension. Although the maximum QRS vector in the horizontal projection is not abnormal, the QRS loop area is outside the normal range.

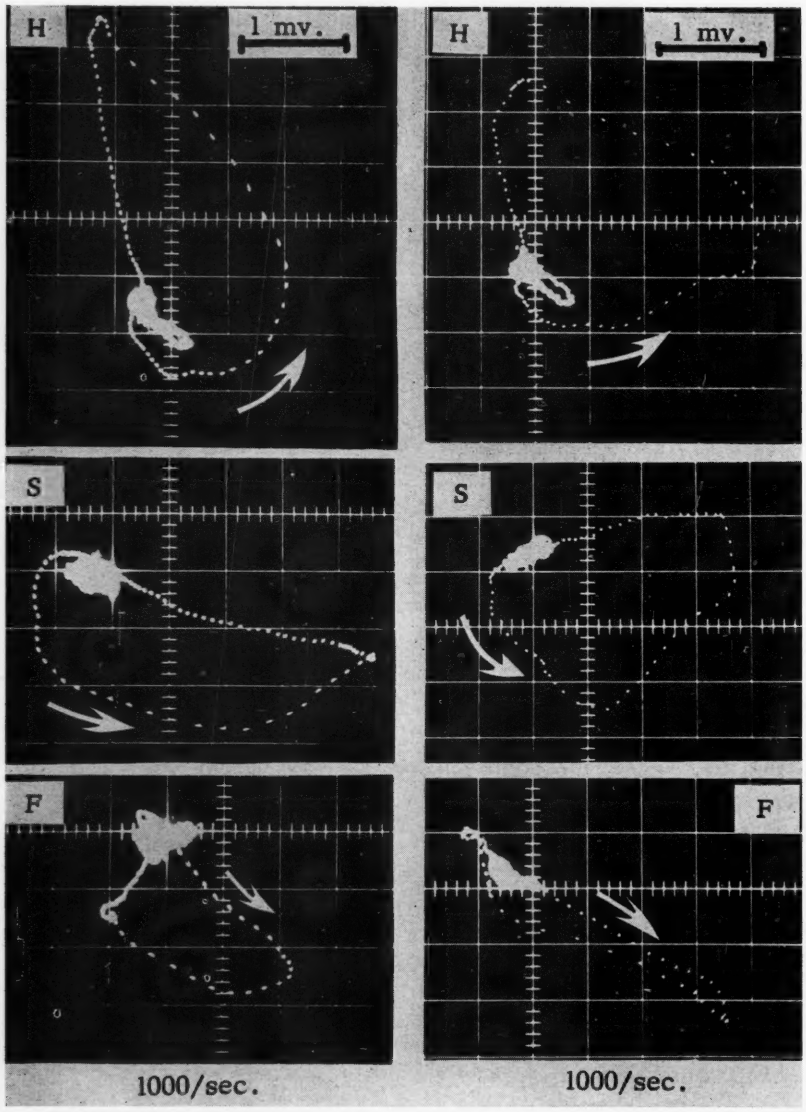


Fig. 5. *Left:* VCG from a 16-year-old boy with congenital aortic stenosis and a moderate pressure gradient across the aortic valve. The QRS loops are not qualitatively abnormal. However, the maximum QRS vectors and loop areas are above normal in the horizontal and sagittal projections. *Right:* Record from a 15-year-old boy with congenital aortic stenosis. The QRS loop is normal in appearance, but loop area is abnormally large in the horizontal and sagittal projections.

tion. The half-area QRS vector angle appears to be a reasonable substitute for determination of the planar mean QRS vector angle in VCGs suspected of showing LVH.

SPATIAL QRS-T ANGLE. The spatial QRS-T angles from three groups of normal subjects who have been studied with corrected lead systems are shown in Table III. The widening of this angle in LVH is apparent, as is the overlap with the normal range.

All patients with LVH who had abnormal spatial QRS-T angles had planar half-area QRS vector–T angles which also fell outside the normal limits.

The similarity of the spatial QRS-T angles with the Frank and SVEC-III systems in studies on normal subjects is noteworthy. This and other evidence would suggest that results with these two methods will be quite similar.

COMPARISONS OF NORMAL SUBJECTS AND PATIENTS WITH LVH AS POPULATIONS. There were two problems in comparing these two

groups as population samples. First, many of the LVH measurements were not normally distributed, making standard statistical comparison invalid. Second, the normal group previously studied included very few people who were in the age ranges of 15 to 20 and 50 to 60 years. In an attempt to circumvent these problems, and yet determine whether most or all of the patients with LVH did represent a different vectorcardiographic population, we compared individuals in the LVH and normal groups by nonparametric methods.

Subjects were chosen from the two groups who were within 1 year of age of each other and of the same sex. Nineteen pairs of individuals met these age and sex requirements, with ages ranging from 18 to 60 years. The Wilcoxon signed rank test[11] was used in the evaluation of seven measurements in each projection of the VCG. The probability values for the two-sided proposition are shown in Table IV. The parameters which had poor probability values were expected, i.e., the maximum QRS vector angle in the horizontal projection, and results for T magnitude. The other values were satisfactorily significant.

The results are interpreted as indicating that the patients with LVH and the normal subjects were representative of vectorcardiographically different and separable populations.

ELECTROCARDIOGRAPHIC COMPARISON. Standard electrocardiograms were not obtained at the time of the vectorcardiographic examination. Electrocardiograms were recorded in 37 of the 41 patients within 3 months of the date of the VCG, and these records were analyzed in detail for evidence of LVH. The eight criteria outlined by Chou and associates[12] were used; these include several voltage, frontal axis, and S-T-T criteria.

The electrocardiograms of 3 patients failed to meet any criteria. The VCGs of these 3 patients displayed increased QRS voltage, and two showed T abnormalities as well. In 6 other cases, one electrocardiographic criterion was fulfilled in each; in 4 cases this was a delayed intrinsicoid deflection in the left precordial leads. All of these patients had multiple vectorcardiographic abnormalities, which in-

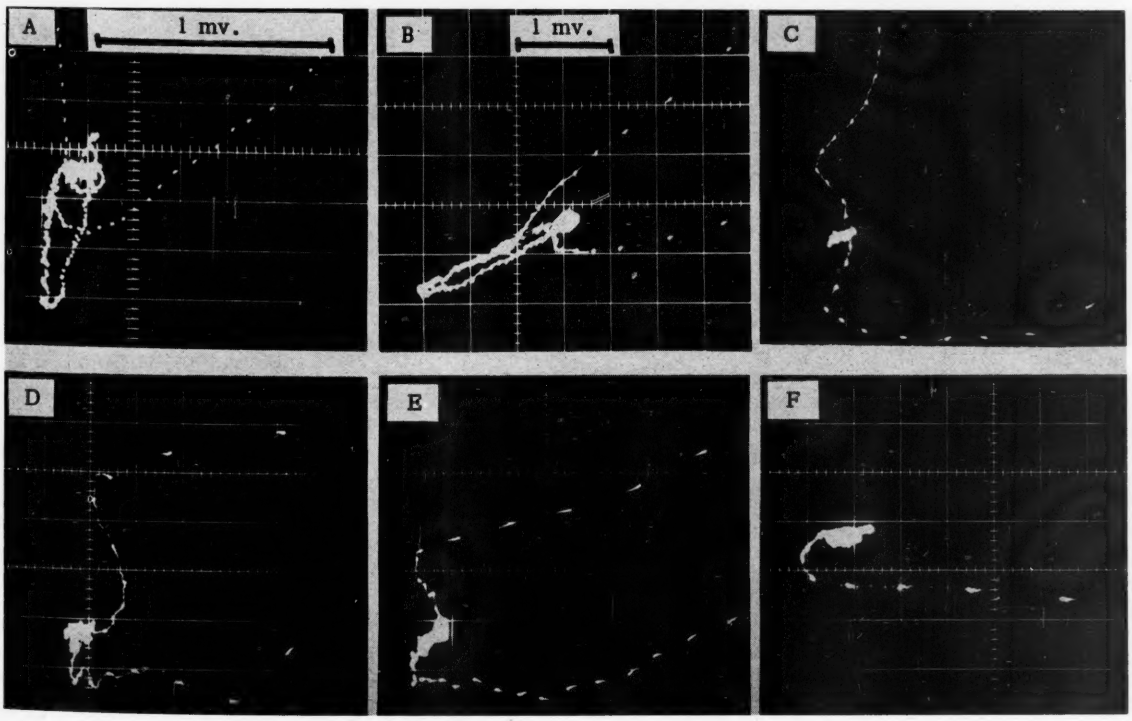


Fig. *6*. Horizontal plane views of the central part of the QRS loop in 6 patients with LVH. In *A* and *B* the QRS and T complexes have been recorded. In *C* through *F*, only the QRS loops are shown. Initial anterior forces are evident in each case, a finding present in 40 of 41 patients. Examples *C, D, E,* and *F* are similar in voltage calibration to *A*.

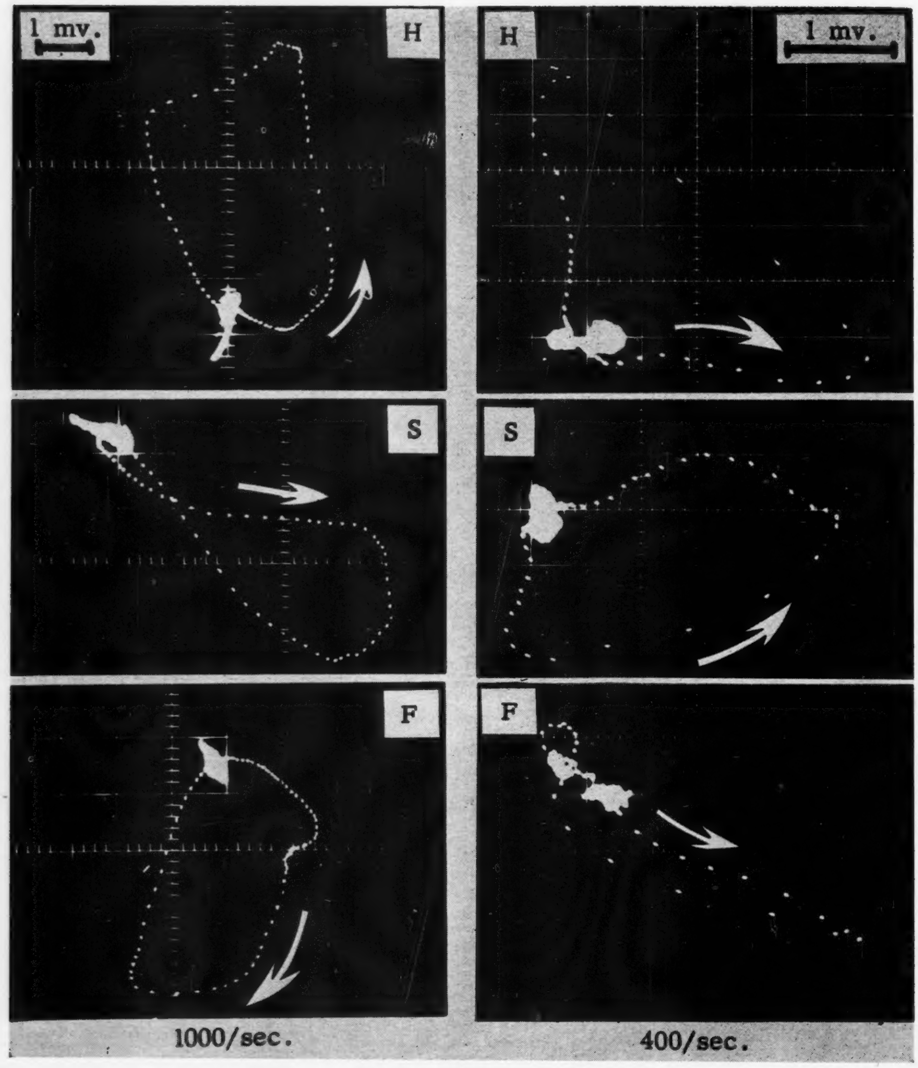


Fig. 7. Two unusual VCGs from patients with LVH. *Left:* Record from a 14-year-old boy with supravalvular stenosis of the aorta. The patient weighed 138 pounds, and at autopsy, severe LVH was found. The left ventricular wall was 4.5 cm. in thickness, and the heart weighed 860 grams. Notable features in the VCG are the very great voltage and the vertical orientation of the QRS loop as seen in the frontal projection. *Right:* VCG in a 30-year-old woman with coarctation of the aorta. The configuration of the QRS loop in the horizontal projection is unusual. An S-T vector is present and directed to the right and superiorly.

cluded alterations of QRS position or magnitude in each case.

These results suggest that vectorcardiographic display of Frank leads provides a more sensitive indication of LVH than do present electrocardiographic criteria.

FALSE POSITIVITY. The incidence of false positive diagnoses has been a major obstacle in determining satisfactory electrocardiographic criteria for LVH. The frequency of this error with the VCG was sought by comparing the individual VCGs from our normal group with the normal statistical limits previously determined from them. The parameters tested were the QRS area and the maximum QRS vector magnitude in each projection, making a total of six comparisons of magnitude per patient. It would be expected that the findings in approximately 2.5 per cent of normal people would exceed normal limits. This could mean, however, that for *each parameter* the findings in 2.5 per cent of normal people would be above

limits. A given group without LVH could include subjects with one "abnormality" each, and, thus, 15 per cent could qualify for high voltage in one measurement (6 parameters with 2.5 per cent each).

When this test was performed, 8 of the 72 normal subjects had at least one measurement of QRS loop magnitude outside the normal range. Seven of the 8 had two or more "abnormalities," with two being the most common number.

If the limits of normal are expanded to include the absolute ranges of values found in the normal subjects, significant loss of abnormalities from the LVH group occurs. Closer scrutiny of these 8 individuals permits tentative exclusion of 4 of them from a vectorcardiographic diagnosis of LVH because of QRS loop positions outside the absolute ranges observed with LVH. It is possible that a slightly wider range of QRS loop locations will be found in LVH as more patients are examined. However, through use of the observations herein employed there is a possibility of a false positive diagnosis of LVH in approximately 6 per cent of normal subjects when QRS magnitude data alone are employed.

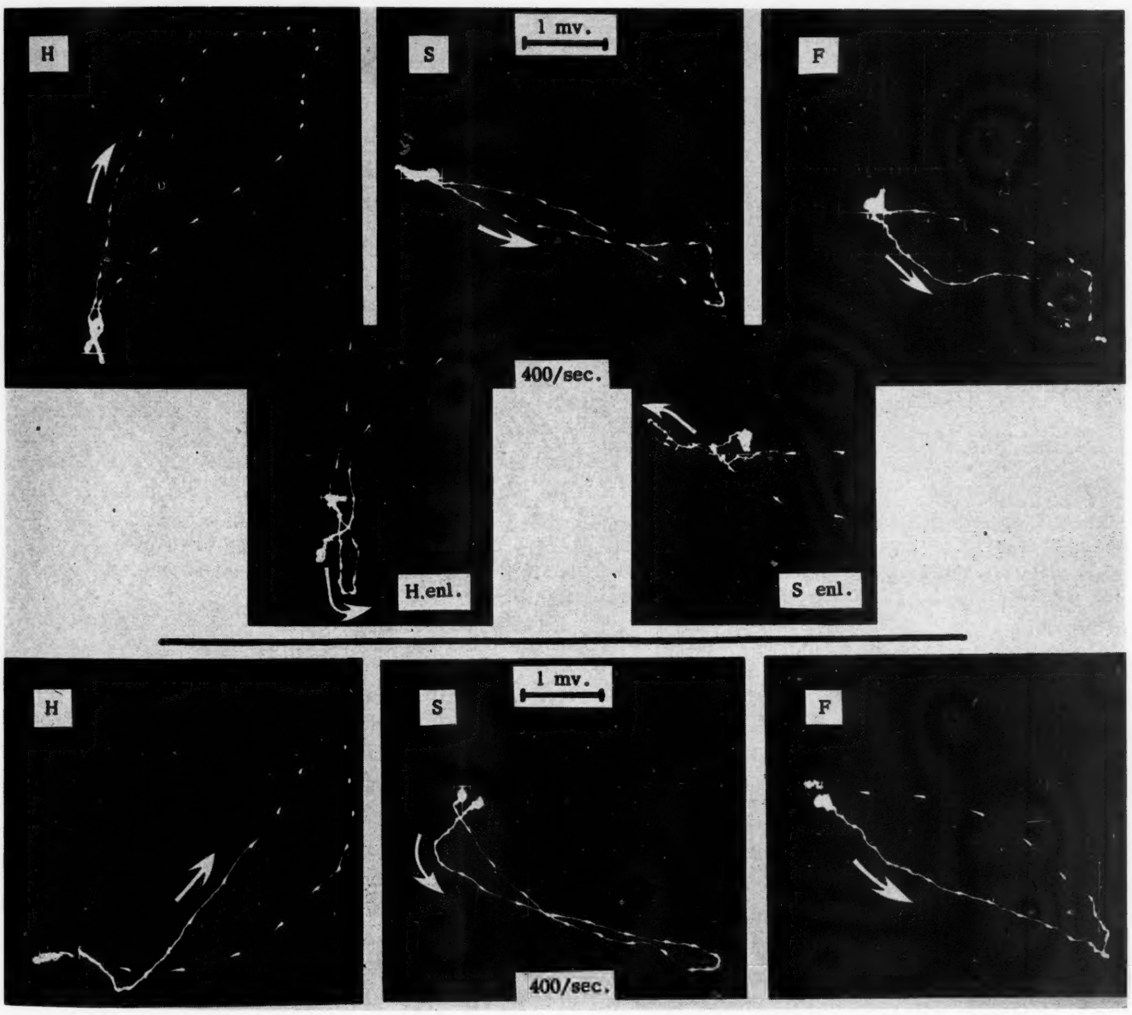


Fig. 8. Two examples of unusual inscription in the horizontal projection. The QRS loops alone have been recorded. *Above:* Record from a 24-year-old man with aortic regurgitation. After a transient anterior deflection the beam abruptly turns posteriorly and to the right, resulting in clockwise inscription in the horizontal plane. Such a finding could be the result of anterolateral infarction, although there is no clinical evidence of this in the patient. *H. enl.:* Enlarged view of horizontal projection. *S. enl.:* Enlarged sagittal projection. *Below:* VCG from a 22-year-old girl with subaortic stenosis. Clockwise inscription is seen in the horizontal projection after counterclockwise inscription of initial forces. Abnormal voltage is present in both records.

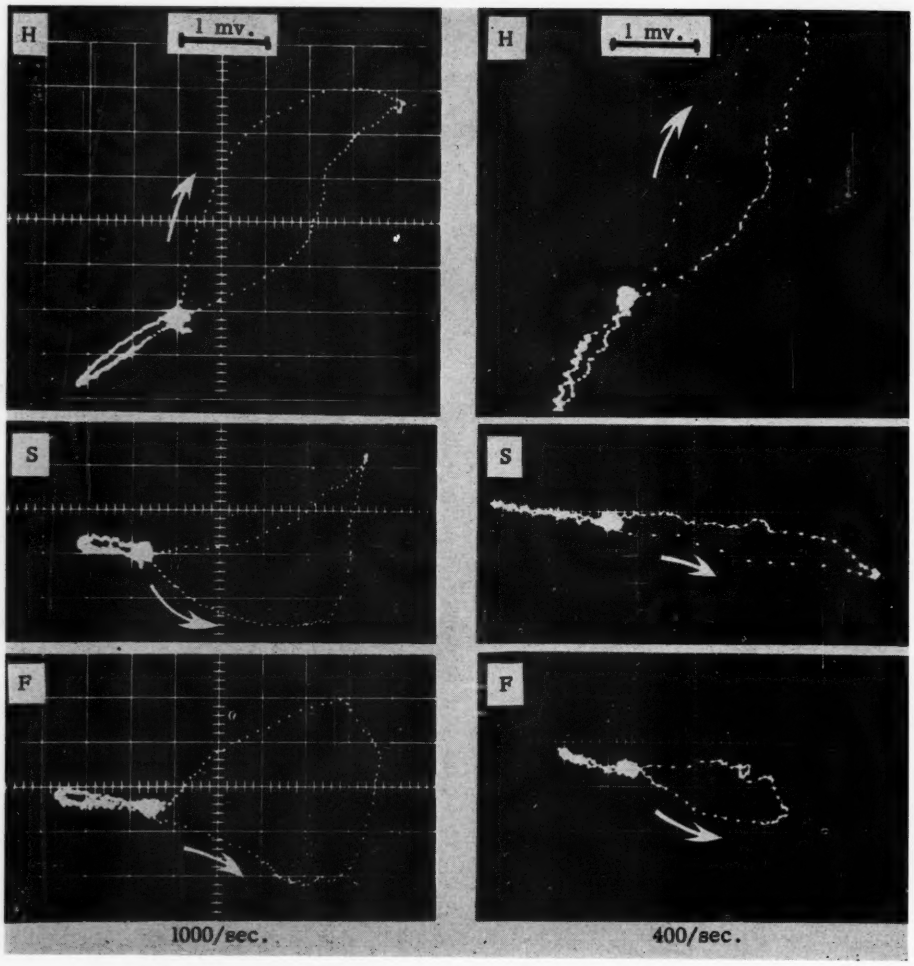


Fig. 9. Two records of left bundle branch block. *Left:* 40-year-old woman with aortic stenosis and regurgitation. *Right:* 56-year-old man with aortic stenosis. In both cases the QRS and T loops are discordant. Conduction delay is evident and an abnormal direction of inscription is seen in the horizontal projection.

It should be added that these normal VCGs were not far outside the statistically established tentative normal ranges, and that diagnostic accuracy will increase markedly when magnitude values exceed the normal by more than approximately 30 per cent. In the individual VCG, considerable supporting evidence for LVH will be found with associated abnormalities of T loop and QRS-T angle.

Observation of the thickness of the chest wall remains an important consideration when voltage criteria alone are employed. A striking example was seen in a man who had no heart disease, was 66 inches tall, and weighed 97 pounds. His VCG demonstrated marked increases above normal in QRS loop area, which could be falsely interpreted as representing LVH.

There is a possibility that a higher incidence of false positive diagnosis will be found in the subjects who are in the age range of 15 to 20 years, since the age range of subjects in the normal control group began at 19 years. Preliminary data from normal children suggest that this will not be the case, however.

*Left bundle branch block.* Five patients met electrocardiographic and vectorcardiographic criteria for LBBB. Four had advanced rheumatic aortic valvular disease and 1 died from coarctation of the aorta. Examples are shown in Fig. 9.

## Discussion

Ideal electrocardiographic or vectorcardiographic criteria for LVH would be those with little or no overlap with the normal

population and with no resemblance to other abnormalities. For this reason, emphasis in this study was placed on alterations in the QRS loop, with a desire to avoid the lack of specificity of QRS-T angle and T loop abnormalities. These were common in our patients, but it is important to note that they did not occur as isolated findings without alterations in the QRS loop. A VCG which demonstrates no QRS abnormality would appear to have little chance of indicating LVH.

The Frank VCG is a sensitive means of diagnosing LVH, and it is suspected that additional study will prove its superiority to the standard electrocardiogram in this respect. However, the incidence of false positive diagnoses due to high voltage in some of the normal subjects is somewhat disappointing. When several parameters are measured and a diagnosis is suspected on the basis of the observation of one abnormality, some degree of false positivity seems unavoidable. At present, if voltage above our tentative normal range is used as a diagnostic criterion, it appears that there will be a minimum chance of overdiagnosis in about 6 per cent of the people who do not have LVH. This is a lower incidence of positive error than most electrocardiographic studies have claimed.

The presence of initial anterior forces in all but one patient with LVH is noteworthy. Tiny or absent R waves in the right and mid-precordial leads of the electrocardiogram pose a difficult problem in excluding anteroseptal myocardial infarction in some patients with LVH. The orthogonal VCG should prove to be of aid by demonstrating initial anterior positivity in such patients and thereby helping to exclude infarction. The dependability of this sign will require proof by clinicopathologic correlations.

The cases studied represented various grades of severity of physiologic abnormality. Teen-age patients with systolic gradients of from 25 to 50 mm. across the aortic valve are included as mild examples, as well as other patients with extreme disability. It appears that there is an electrical evolution of LVH which begins with changes in the magnitude and position of the QRS loop. Movement of the T axis anteriorly and to the right follows, and LBBB will eventually develop in some patients as the end-stage electrical pattern of LVH.

Finally, it should be emphasized that the ranges in voltage which are described can be applied with certainty only in VCGs obtained with the Frank lead system. Although observations strongly suggest close correspondence between the SVEC-III and Frank methods,[13,14] additional study with pathologic groups by the two methods is needed before it can be concluded that QRS magnitude data are interchangeable.

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# Studies of blood pressure, heart rate, and the electrocardiogram in adult twins

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The demonstration of heredity as a predisposing factor to different forms of cardiovascular disease[1-3] indicates a need for determining the relative importance of hereditary influence upon the variability of different physiologic processes relating to cardiac function. For this, the initial problem is to determine whether measured variation in such processes has a discernible hereditary component. Studies of blood pressures in twins have been employed for this purpose,[4-8] and electrocardiographic patterns and heart dimensions have been compared in identical and fraternal twins.[9,10] In the study on twins which we are reporting here a number of different measurements of cardiac function have been taken under uniform conditions in the same adult subjects; this permits a comparative evaluation of the relative importance of genetically conditioned variability in different measurements which are used clinically to describe cardiac function.

## The study sample

The 53 pairs of twins utilized in this analysis consist of 34 monozygotic (MZ) pairs (14 male, and 20 female pairs), and 19 like-sex dizygotic (DZ) pairs (5 male and 14 female pairs). All subjects were over 18 years of age, with a mean age of 25.4 years for males, and 29.5 years for females. In each category of sex and zygosity the age distributions were comparable, and, since the analysis is based upon the differences within the pairs of twins, in whom age is identical, the effect of age upon the studies is minimized. On the basis of history, physical examination, and laboratory work-up, all subjects were judged to be in good general health. The methods of diagnosis of zygosity as well as the physical and socioeconomic description of the subjects have been previously presented.[11]

## Methods

The two members of each pair of twins were scheduled for simultaneous studies. In 6 instances (4 MZ and 2 DZ pairs) it was not possible to study both members of the pair of twins on the same day, but since the conditions of study were standardized and were uniform for the two members of each of these pairs, and since the differences within the pair in these individuals were not significantly dissimilar to those within the other pairs studied, they were included in the present analysis.

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The subjects came to the laboratory in a fasting state, and every effort was made to maintain the basal state during the entire procedure. After a resting period of 30 minutes, 4 ballistocardiograms (BCG) and simultaneous electrocardiograms (ECG), utilizing the 3 standard limb leads, were taken over a period of 10 minutes. At the end of the procedure, a routine 12-lead electrocardiogram was taken on each subject. Blood pressure and pulse rates were recorded at 1-minute intervals, beginning 10 minutes before the first ballistocardiogram and continuing throughout the procedure. The blood pressure was determined by means of the standard arm cuff and mercury manometer, utilizing the first appearance of sounds as the systolic pressure and the disappearance of the sounds as the diastolic pressure. The blood pressure readings obtained during the final 10 minutes were averaged, and the average systolic and diastolic pressures were used in the statistical analysis. The heart rates used in the analysis were obtained from the ballistocardiographic and simultaneous electrocardiographic tracings. Pulse rates were also obtained from the routine 12-lead electrocardiograms, and these were used in the analysis to determine any differences between those taken under strictly basal conditions and those under slightly less basal conditions. The electrocardiograms were compared for the general form of the complexes with measurements of QRS, Q-T, and P-R intervals, and heart rate being made in Lead II of the routine tracings. All of the measurements were made individually and later paired to determine intrapair differences. The diagnosis of zygosity was applied just prior to the statistical analysis.

The statistical method used is based upon a paired analysis.[11] The average of the differences between the two members of the pairs of twins have been expressed as mean intrapair variances in which the mean intrapair variance is: $\Sigma\ x^2/2n$, where x is the difference between the two members of a pair of twins, and n is equal to the number of pairs of twins. The F distribution is used to obtain the probability level of the ratios of the different mean variances.

To permit a comparison of the mean of the differences between the two members of the pairs of twins to the mean of the differences expected to occur between two unrelated individuals in the study population, mean interpair variances have been calculated. The mean interpair variances,

$$s^2 = [\Sigma\ x^2 - (\Sigma\ x)^2/n]/n-1,$$

are calculated from the average of the values for the two members of each pair of twins. These variances are multiplied by two to make them comparable to the mean intrapair variances, and the F distribution is used to obtain the probability level of the ratios of different mean interpair and intrapair variances. In the comparison of monozygotic and dizygotic mean intrapair variances, and intrapair and interpair variances, a one-tail test of significance will be given; when comparisons between the sexes are made, a two-tail test is required.

In the analysis which follows, certain features which characterize data on twins are of particular importance. Monozygotic mean intrapair variances represent the average of the differences between genetically identical individuals who have had the similarity of life history and environment which this genetic relationship and common home environment impose. Dizygotic twins differ in their genetic relationships as do ordinary brothers and sisters; on the average, they differ in one half of their total genetic endowment. The similarity of life history and environment in dizygotic twins, in so far as these are dependent upon maternal age, history of pregnancy and parity, and a common home environment, is comparable to that of monozygotic twins. When these influences differ excessively from those for monozygotic twins, they must be presumed to relate either directly or indirectly to the genetic differences between the two members of dizygotic pairs (with the exception of particular prenatal factors which may differ for the two types of twins.[12] However, selection of pairs on the basis of health status should reduce the seriousness of the latter influences in the present data.[11] Mean interpair variances represent the average of the differences between unrelated individuals with the genetic and environmental dissimilarity which characterizes this study population.

*Table* I. *Individual* ranges, averages, and standard deviations of basal measurements*

| | *Males* | | | | *Females* | | | |
|---|---|---|---|---|---|---|---|---|
| | *n* | *Range* | *Mean* | *S.D.* | *n* | *Range* | *Mean* | *S.D.* |
| Systolic pressure (mm. Hg) | 19 | 94–137 | 113.21 | 12.71 | 34 | 87–128 | 109.24 | 9.35 |
| Diastolic pressure (mm. Hg) | 19 | 64–94 | 77.32 | 7.73 | 34 | 49–91 | 76.41 | 8.85 |
| Heart rate† (BCG) (beats/min.) | 19 | 47–90 | 62.21 | 9.04 | 34 | 54–99 | 70.76 | 9.20 |
| Heart rate† (ECG) (beats/min.) | 19 | 47–84 | 63.58 | 8.96 | 34 | 55–111 | 72.59 | 13.86 |
| P-R interval (sec.) | 19 | 0.13–0.20 | 0.166 | 0.020 | 34 | 0.12–0.20 | 0.163 | 0.023 |
| QRS interval (sec.) | 19 | 0.04–0.08 | 0.065 | 0.015 | 34 | 0.04–0.10 | 0.061 | 0.019 |
| Q-T interval (sec.) | 19 | 0.28–0.43 | 0.362 | 0.033 | 34 | 0.28–0.44 | 0.367 | 0.039 |

*One individual of each pair of twins taken at random.
†Males and females differ significantly, $p < 0.01$.

## Results

The ranges, means, and standard deviations of the measurements analyzed are given for males and females in Table I. These values are based upon one member of each pair of twins taken at random to provide a description of the study population. As would be anticipated in a population free of any clinically discernible condition which may adversely influence the observation, all values are within commonly defined "normal" limits. The mean interpair and intrapair variances for the blood pressure and heart rate, their variance ratios, and the probability levels of these ratios are presented in Table II. The MZ interpair:intrapair variance ratios for systolic, diastolic, and mean pressures are statistically significant in females, but not in males. In males, the MZ and DZ interpair:intrapair variance ratios for heart rate are statistically significant, but neither comparison is significant in females. These findings are consistent with the comparison of monozygotic and dizygotic intrapair variances in males and females. Whereas in males the monozygotic blood pressure variances even exceed the dizygotic variances, in females the MZ:DZ intrapair variance ratios are statistically significant for systolic pressure and mean pressure; the diastolic ratio falls short of the 5 per cent level. In females a significant component of genetic variability is measured at least for systolic and mean pressure. It appears that basal blood pressure is subject to greater environmental influence in males than in females. When the monozygotic mean intrapair variance of males and females is compared, the male variances are consistently larger than the female variances, and significantly larger for systolic pressure (F ratio = 3.61, $p > 0.005$).

The sex difference in both the monozygotic and dizygotic intrapair variance ratios for heart rate (like the interpair: intrapair variance ratios), differs markedly from that in both for blood pressure. Neither the male nor the female MZ:DZ intrapair variance ratios are statistically significant for heart rate, but, unlike the situation for blood pressure, the male monozygotic intrapair variance is smaller

than that of the female, and when considered with the interpair:intrapair variance ratios suggests that environmental influences may be a relatively more important factor in the heart rate of females than of males.

The results of the electrocardiographic studies are presented in Table III. Both QRS and Q-T intervals provide large and highly significant monozygotic interpair: intrapair ratios. Large and highly significant female MZ:DZ ratios are also found which suggest a strong genetic component of variability for these two variables—stronger than for any of the other variables analyzed. The comparability of the male and female monozygotic intrapair variances of the monozygotic interpair:intrapair variance ratios indicate that with a larger male dizygotic sample similar findings might be anticipated for males.

Heart rate and P-R interval stand in marked contrast to QRS and Q-T intervals, both in terms of measured genetic variability and sex influence. The heart rate variances given in Table III also differ rather markedly from the heart rate variances in Table II. With the exception of male monozygotic interpair and female monozygotic intrapair variances, the variances are larger than those calculated at the time of the electrocardiogram. The ECG followed the BCG, and apparently the departure from the basal conditions which prevailed at the time at which the latter was recorded influenced heart rate. The differential change in heart rate suggests that there may also be a demonstrable genetic and sex-influenced factor in the lability of heart rate. The female monozygotic interpair heart rate variance which in Table II was slightly smaller than that observed for males is now significantly greater than male variance (F ratio = 3.41, $p > 0.025$). Both the female MZ and the female DZ interpair heart rate variances, when taken at the time of the ECG, are significantly greater, $p > 0.025$, than when taken at the time of the BCG.

From Table III it is apparent that genetic variability in the ECG pattern can be measured objectively by QRS and Q-T intervals in females. Presumably, this would also be true in males with a larger sample of dizygotic male twins. Moreover, from the analysis of heart rate it is apparent that not only are the conditions of study important, but that by changing the conditions of study it may be possible as well to demonstrate sex and genetically conditioned differences in heart rate lability.

## Interrelation of measurements

The interrelation or association between measurements is frequently of great importance. In twins it is possible in some instances to examine the nature of the interrelation between measurements by a "cross-twin" analysis. By this method the correlation between measurement A and measurement B in the same individual is compared to the correlation between measurement A in one twin and measurement B in the co-twin. When the within-individual correlation is compared to the monozygotic cross-twin correlation, the relative strength of the within-individual mechanical and physiologic environment upon the interrelation of the two measurements can then be assessed. Since the within-individual environment is excluded in the cross-twin correlation, any correlation of measurements is the consequence of either the genetic or environmental influences, or both, which act similarly upon the two traits in the two different but genetically identical individuals. Similar cross-twin correlations with dizygotic twins make it possible to further evaluate the monozygotic cross-twin correlations for the genetic and environmental basis of the observed relationships. The statistic used for the cross-twin analysis is the correlation coefficient. When the correlation coefficient is employed, particularly in small samples, it is necessary to base conclusions upon the calculated probabilities, rather than upon the magnitude of the correlation coefficients. Evaluation of the relative sizes of different correlations should be based upon values of z.[13] In view of the fact that correlations which compare a part with the whole, or one measurement with another, from which it is partially derived are not meaningful, only certain correlations are possible with the present data. For example, correlations of systolic or diastolic pressure with mean pressure would not be meaningful. The

*Table* II. *Mean interpair and mean intrapair variances for monozygotic and dizygotic twins*

| Zygosity | Comparison | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | *Variance* | *F ratio* | *p* | *n* | *Variance* | *F ratio* | *p* |
| | | | | *Systolic Pressure* | | | | | |
| MZ | Interpair | 13 | 127.70 | | | 19 | 106.52 | | |
| | Inter:Intra | | | 1.43 | >0.25 | | | 4.30 | 0.001 |
| MZ | Intrapair* | 14 | 89.54 | | | 20 | 24.78 | | |
| | MZ:DZ | | | 0.73 | <0.75 | | | 2.29 | <0.05 |
| DZ | Intrapair | 5 | 65.00 | | | 14 | 56.75 | | |
| | Intra:Inter | | | 2.41 | <0.25 | | | 1.91 | <0.25 |
| DZ | Interpair | 4 | 156.50 | | | 13 | 108.62 | | |
| | | | | *Diastolic Pressure* | | | | | |
| MZ | Interpair | 13 | 74.16 | | | 19 | 136.64 | | |
| | Inter:Intra | | | 1.42 | >0.25 | | | 5.07 | <0.001 |
| MZ | Intrapair | 14 | 52.11 | | | 20 | 26.93 | | |
| | MZ:DZ | | | 0.33 | <0.75 | | | 2.14 | >0.05 |
| DZ | Intrapair | 5 | 17.20 | | | 14 | 57.71 | | |
| | Intra:Inter | | | 1.60 | >0.25 | | | 0.98 | <0.75 |
| DZ | Interpair | 4 | 27.50 | | | 13 | 56.76 | | |
| | | | | *Mean Pressure* | | | | | |
| MZ | Interpair | 13 | 79.24 | | | 19 | 134.93 | | |
| | Inter:Intra | | | 1.42 | >0.25 | | | 6.10 | <0.001 |
| MZ | Intrapair | 14 | 55.87 | | | 20 | 22.11 | | |
| | MZ:DZ | | | 0.49 | >0.75 | | | 2.46 | >0.025 |
| DZ | Intrapair | 5 | 27.39 | | | 14 | 54.50 | | |
| | Intra:Inter | | | 3.02 | >0.10 | | | 1.12 | >0.25 |
| DZ | Interpair | 4 | 82.85 | | | 13 | 61.30 | | |
| | | | | *Heart Rate* | | | | | |
| MZ | Interpair | 13 | 127.54 | | | 19 | 119.37 | | |
| | Inter:Intra | | | 4.83 | <0.005 | | | 2.27 | <0.05 |
| MZ | Intrapair | 14 | 26.43 | | | 20 | 52.60 | | |
| | MZ:DZ | | | 0.19 | >0.95 | | | 0.98 | <0.75 |
| DZ | Intrapair | 5 | 5.10 | | | 14 | 51.54 | | |
| | Intra:Inter | | | 9.22 | <0.025 | | | 1.25 | >0.25 |
| DZ | Interpair | 4 | 47.00 | | | 13 | 64.31 | | |

*The male monozygotic intrapair variance is significantly larger than the female monozygotic intrapair variance (F ratio = 3.61, p > 0.005).

The greater than (>) or less than (<) sign is applied to the nearest percentage point given by Pearson and Hartley (1956): 0.25, 0.10, 0.05, 0.025, 0.01, 0.005, 0.001.

MZ: Monozygotic. DZ: Dizygotic.

*Table III. Electrocardiogram. Mean interpair and mean intrapair variances for monozygotic and dizygotic twins*

| Zygosity | Comparison | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | *n* | *Variance* | *F ratio* | *p* | *n* | *Variance* | *F ratio* | *p* |
| | | | | *Heart Rate* | | | | | |
| MZ | Interpair* | 12 | 88.50 | | | 19 | 302.00 | | |
| | Inter:Intra | | | 2.98 | >0.025 | | | 6.42 | <0.001 |
| MZ | Intrapair | 13 | 29.65 | | | 20 | 47.05 | | |
| | MZ:DZ | | | 0.29 | >0.90 | | | 1.31 | >0.25 |
| DZ | Intrapair | 5 | 8.60 | | | 14 | 61.57 | | |
| | Intra:Inter | | | 20.29 | <0.005 | | | 3.96 | <0.01 |
| DZ | Interpair | 4 | 174.50 | | | 13 | 243.54 | | |
| | | | | *P-R Interval* | | | | | |
| MZ | Interpair | 13 | 0.631 | | | 19 | 0.822 | | |
| | Inter:Intra | | | 2.57 | 0.05 | | | 3.04 | <0.01 |
| MZ | Intrapair | 14 | 0.246 | | | 20 | 0.270 | | |
| | MZ:DZ | | | 0.28 | >0.90 | | | 1.64 | >0.25 |
| DZ | Intrapair | 5 | 0.070 | | | 14 | 0.442 | | |
| | Intra:Inter | | | 5.14 | >0.05 | | | 1.40 | >0.25 |
| DZ | Interpair | 4 | 0.360 | | | 13 | 0.620 | | |
| | | | | *QRS Interval* | | | | | |
| MZ | Interpair | 13 | 0.384 | | | 19 | 0.136 | | |
| | Inter:Intra | | | 7.25 | <0.001 | | | 2.62 | <0.025 |
| MZ | Intrapair | 14 | 0.053 | | | 20 | 0.052 | | |
| | MZ:DZ | | | 0.38 | <0.90 | | | 8.17 | <0.001 |
| DZ | Intrapair | 5 | 0.020 | | | 14 | 0.425 | | |
| | Intra:Inter | | | 18.00 | <0.005 | | | 0.85 | <0.75 |
| DZ | Interpair | 4 | 0.360 | | | 13 | 0.360 | | |
| | | | | *Q-T Interval* | | | | | |
| MZ | Interpair | 13 | 2.184 | | | 19 | 2.072 | | |
| | Inter:Intra | | | 12.00 | <0.001 | | | 11.84 | <0.001 |
| MZ | Intrapair | 14 | 0.182 | | | 20 | 0.175 | | |
| | MZ:DZ | | | 0.60 | <0.75 | | | 5.04 | <0.001 |
| DZ | Intrapair | 5 | 0.110 | | | 14 | 0.882 | | |
| | Intra:Inter | | | 4.18 | <0.10 | | | 1.59 | <0.25 |
| DZ | Interpair | 4 | 0.460 | | | 13 | 1.400 | | |

*Female monozygotic variance is significantly larger than the male monozygotic variance (F ratio = 3.41, $p > 0.025$).

*Table IV. Correlations between systolic and diastolic pressure*

| *Sex* | *Zygosity* | *Comparison* | *n* | *r* | *t*† | *p* |
|---|---|---|---|---|---|---|
| M | MZ | Individual | 14 | 0.788**** | 2.50 | 0.01–0.02 |
| | | Cross-twin | 14 | 0.001 | | |
| F | MZ | Individual | 20 | 0.884**** | 2.26 | 0.02–0.05 |
| | | Cross-twin | 20 | 0.550* | | |
| | | | | | 1.45 | 0.10–0.20 |
| F | DZ | Cross-twin | 14 | 0.056 | 3.02 | 0.002–0.005 |
| | | Individual | 14 | 0.873**** | | |

*p 0.05. **p 0.01. ***p 0.005. ****p 0.001.
†t is calculated for the difference of the values of z.

correlations calculated are systolic pressure, diastolic pressure, mean pressure, QRS, and P-R with heart rate. Correlations were also made for systolic and diastolic pressures, and for QRS and P-R intervals.

The within-individual correlations of systolic, diastolic, and mean pressures with heart rate were moderate but not statistically significant. In females, the heart rate with P-R gave a correlation of $-0.521$, $p = 0.01-0.02$, and with QRS a moderate but not statistically significant negative correlation was obtained. The positive within-individual correlations of QRS with P-R were not significant; the correlations of systolic pressure with QRS and P-R were essentially zero. Only between systolic and diastolic pressure were the within-individual correlations significant in both males and females.

In female monozygotic and dizygotic individuals, and in male monozygotic individuals, the within-individual correlations of systolic with diastolic pressure deviate significantly from $p = 0$ (Table IV). The male monozygotic cross-twin correlation is essentially zero, indicating that the significant male monozygotic within-individual correlation is due most importantly to mechanical and physiologic factors in the individual environment. In females, on the other hand, although the significant difference between the monozygotic individual and cross-twin correlations indicates, as in males, that the within-individual environment has an influence upon the relationship of systolic and diastolic pressure, the fact that the monozygotic cross-twin correlation is significant indicates that there are additional factors which influence this relationship. Even though the difference between the monozygotic and dizygotic cross-twin correlations is not significant in these data, it strongly suggests that the relationship of systolic and diastolic pressure in females, at least, is genetically influenced. The difference between males and females in this association of systolic and diastolic pressure is in accordance with the variance analysis (Table II), in which it appeared that the genetic influence upon blood pressure was stronger in females than in males.

## Comment

In the present analysis it has been possible to demonstrate a genetic component of variability within the normal range of a number of different measurements of cardiac function under basal conditions. On a comparative basis, QRS, Q-T, mean pressure, systolic pressure, and diastolic pressure appear, in this order, to be genetically influenced. Genetic interpretation throughout rests most heavily upon the female subjects, but the similarity of the male and female monozygotic variances for QRS and Q-T indicate that, at least for these two measurements, genetically conditioned variability may be comparably expressed in the two sexes. In the other variables, sex is found to play an impor-

tant role in the expression of genetically conditioned variability. There was no evidence of a genetic component of variability for heart rate or pulse pressure in the present data. In comparing heart rate variances of males and females, and for heart rate obtained at the time of the BCG and ECG, it appears that heart rate is more readily modified by environmental factors in females than in males, and that the relative lability of heart rate may be under genetic control.

The mean monozygotic intrapair variances of males is larger than that of females for both systolic and diastolic pressure, and this difference is statistically significant in the case of systolic pressure. A similar sex difference was reported by Hines and associates[8] in a study of hypertensive vascular disease in twins. When identical twins "were females, the hypertensive vascular disease was of about the same degree of severity and the blood pressures were in about the same range of elevation. In contrast, when the twins were males, one twin usually had much more severe hypertensive vascular changes and had died at an earlier age than the other twin."[8] In the present study, in the case of normal blood pressures, male monozygotic twins differ more than do female monozygotic twins.

The influence of sex on blood pressure is further demonstrated by the cross-twin analysis. In female monozygotic twins the cross-twin correlation between systolic and diastolic blood pressure is statistically significant, $r = 0.550$, $p = 0.02$, whereas in males this correlation is zero. Bøe and co-workers[14] have also noted that the correlation of systolic and diastolic pressure is "generally better in females than in males." The cross-twin correlation employed here implies that the sex difference may actually represent modification of a genetically conditioned relationship of systolic and diastolic pressure.

These data on adult twins imply, as do family studies,[15,16] that genetic influences account for a relatively minor proportion of the variability observed in normal blood pressure. However, the conclusions drawn from these data on twins depart in one important respect from those derived from family studies. Pickering[17] states that "the independence of sex so far as inheritance is concerned is another simplification for it is unnecessary to separate fathers from mothers, brothers from sisters, or sons from daughters." The evidence in twins indicates that such a separation of the sexes is necessary for the genetic interpretation of data on blood pressure. A more complete discussion is presented in a separate communication.[18]

**Summary**

Studies of blood pressure, heart rate, and the electrocardiogram have been analyzed for 53 pairs of twins. All subjects were over 18 years of age, and judged to be in good general health on the basis of histories of health, complete medical examinations, and laboratory tests. Every effort was made to maintain the basal state during the course of the study and to assure comparability for the two members of the pairs of twins.

In a comparative analysis of the different measurements taken a strong genetic component of variability was found in the QRS and Q-T intervals of the electrocardiogram. Systolic, diastolic, and mean pressures also gave some indication of genetic variability, but these measurements were found to be most importantly characterized by sex influences.

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# Experimental and laboratory reports

## Effects of isoproterenol on cardiac output and renal function in congestive heart failure

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Isoproterenol is a sympathomimetic amine that produces potent positive inotropic and chronotropic cardiac effects.[1-4] Previous studies have shown that the peripheral vascular effects of isoproterenol differ from the marked vasoconstrictor effects of many of the other sympathomimetic amines in both man[5,7,8] and experimental animals.[4,6,9,10] Since this drug increases cardiac contractility and lowers systemic vascular resistance, an increased cardiac output and lowered peripheral venous pressure regularly occur in both normal man and subjects with congestive heart failure.[5] Several investigators have observed a renal vasodilator action of intravenously infused isoproterenol in experimental animals.[11-13] In this study the cardiovascular and renal effects of intravenously infused isoproterenol were compared in human subjects with congestive heart failure. These studies have been previously reported in part in preliminary form.[14]

### Methods

Twelve male subjects with heart diseases of varied etiologies were selected for study on the basis of clinical findings characteristic of congestive heart failure with edema. The majority of subjects were studied on their second hospital day regardless of the state of digitalization or diuresis. Diuretics were withheld on the day of study. Subjects with third-degree atrioventricular heart block were excluded from the study.

All tests were performed after the subjects had fasted for 10 to 12 hours. To insure adequate hydration, 240 c.c. of water were administered by mouth every 30 minutes for 2½ to 3 hours prior to the determination of renal clearances, and hydration was continued during the study by administration of 100 c.c. of water by mouth each 30 minutes and/or by intravenous infusion of 5 per cent dextrose in water at rates of 3 to 4 c.c. per minute for the duration of the study.

Specimens of urine were collected by an indwelling catheter. The bladder was emptied by injection of 10 ml. of air and aspiration, followed by injection of 20 ml. of distilled water and then 20 ml. of air with expression of any residue by appli-

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cation of suprapubic pressure. The bladder washout procedure did not exceed 1½ minutes.

After a blank 15-minute collection period, a priming dose of 20 to 30 ml. of 10 per cent inulin was given over a 5-minute interval, followed by administration of a mixture of para-aminohippurate (PAH) and inulin by a constant-infusion pump to maintain blood levels of 10 to 20 mg. per cent inulin and 1 to 3 mg. per cent PAH.[15,16] Fifty-five minutes were allowed for equilibration. Control periods consisted of three 15-minute collection periods followed by two or three 15-minute collection periods during intravenous infusion of isoproterenol at rates of 1 to 4 $\gamma$ per minute. This rate of infusion was unassociated with subjective symptoms, except in one subject who experienced anginal pain and a sinus tachycardia of 140/min., which required discontinuance of the study.

*Table* I

| *Subject and diagnosis* | *CI (L./min./M.²)* | | *RBF (c.c./min./M.²)* | | *Mean systemic BP (mm. Hg)* | |
|---|---|---|---|---|---|---|
| | *Control* | *Isuprel* | *Control* | *Isuprel* | *Control* | *Isuprel* |
| R.C. Syphilitic HD; no digitalis | 1.88 | 3.49 | 123 | 148 | 94 | 94 |
| B.K. IMH; on digitalis | 1.46 | 2.30 | 80 | 129 | 118 | 103 |
| E.D. IMH; on digitalis | 1.22 | 2.34 | 208 | 216 | 90 | 88 |
| J.M. ASHD; on digitalis | 2.43 | 3.38 | 238 | 293 | 97 | 92 |
| E.G. ASHD; on digitalis | 1.78 | 2.83 | 557 | 585 | 112 | 101 |
| N.K. H and ASHD; no digitalis | 1.86 | 2.11 | 136 | 141 | 156 | 146 |
| M.B. ASHD; on digitalis | 2.11 | 2.37 | 88 | 98 | 87 | 84 |
| E.B. H and ASHD; no digitalis | 3.91 | 4.22 | 127 | 154 | 137 | 143 |
| L.H. RHD; on digitalis | 1.42 | 1.94 | 80 | 94 | 74 | 71 |
| S.N. RHD; on digitalis | 2.29 | 4.98 | 267 | 327 | 172 | 162 |
| J.S. HCVD; on digitalis | 1.50 | 2.30 | 145 | 149 | 123 | 124 |
| H.J. ASHD; on digitalis | 1.66 | 3.25 | 216 | 322 | 105 | 110 |
| Mean | 1.96 | 2.96 | 189 | 221 | 114 | 110 |
| s | .73 | .93 | 132 | 142 | 30 | 28 |
| t | 4.91 | | 3.665 | | 2.12 | |
| p | <.01 | | <.01 | | <.05 | |

IMH: Idiopathic myocardial hypertrophy. ASHD: Arteriosclerotic heart disease. HCVD: Hypertensive cardiovascular disease BP: Blood pressure. VP: Venous pressure. RBF: Renal blood flow.

$$\text{RBF} = \frac{\text{ERPF c.c./min.}}{1 - \frac{(0.96 \times \text{Hct})}{100}}$$

Analyses for inulin were performed by the method of Handelsman and Drabkin.[17] PAH was determined by the method of Bratton and Marshall as modified by Smith and co-workers.[18] Determinations of sodium were made by a Baird internal standard flame photometer. Piperocaine was used throughout for local anesthesia to avoid interference with determinations of PAH. All renal clearances were corrected for body surface area.

Peripheral venous and brachial intra-arterial pressures were determined by strain gauges and recorded on a multichannel recorder. Mean pressures were obtained by electrical integration. Cardiac outputs were determined from dye-dilution curves after peripheral injection of Evans blue dye, as previously described.[5] Vascular resistance was calculated from the difference of systemic arterial and venous pressures and systemic and renal blood flows.[19]

| *Mean systemic VP (mm. Hg)* | | *SVR (dynes-sec. cm.$^{-5}$ × $10^3$)* | | *RVR (dynes-sec. cm.$^{-5}$ × $10^3$)* | | *RVR/SVR* | |
|---|---|---|---|---|---|---|---|
| *Control* | *Isuprel* | *Control* | *Isuprel* | *Control* | *Isuprel* | *Control* | *Isuprel* |
| 14 | 12 | 1.94 | 1.05 | 29.1 | 24.7 | 15.0 | 23.6 |
| 16 | 15 | 2.74 | 1.50 | 49.8 | 26.7 | 18.2 | 17.8 |
| 13 | 9 | 2.85 | 1.53 | 17.1 | 16.5 | 6.0 | 10.8 |
| 5 | 4 | 1.76 | 1.21 | 17.9 | 14.0 | 10.2 | 11.6 |
| 15 | 14 | 2.64 | 1.50 | 8.4 | 7.2 | 3.2 | 4.8 |
| 15 | 13 | 3.65 | 2.82 | 47.5 | 43.0 | 13.1 | 15.3 |
| 17 | 17 | 1.56 | 1.33 | 37.3 | 32.1 | 23.9 | 24.2 |
| 20 | 14 | 1.61 | 1.52 | 51.4 | 42.5 | 30.4 | 27.5 |
| 15 | 15 | 1.81 | 1.25 | 32.3 | 25.7 | 17.8 | 20.7 |
| 11 | 9 | 3.29 | 1.44 | 28.2 | 21.9 | 8.6 | 15.2 |
| — | — | — | — | — | — | 10.1 | 19.2 |
| — | — | — | — | — | — | 7.7 | 10.2 |
| 14 | 12 | 2.39 | 1.52 | 31.9 | 25.4 | 13.7 | 16.7 |
| 4 | 4 | .75 | .49 | 14.8 | 11.6 | 7.86 | 6.69 |
| 3.40 | | 5.129 | | 3.25 | | 2.91 | |
| <.01 | | <.01 | | <.01 | | <.02 | |

RHD: Rheumatic heart disease. CI: Cardiac index. SVR: Systemic vascular resistance. RVR: Renal vascular resistance.

**Results**

Type of heart disease, state of digitalization, and respective hemodynamic data of individual cases at the time of determination of renal clearances are presented in Table I. The observations of renal function during infusion of isoproterenol in subjects with congestive heart failure are listed in Table II. Cardiac output and renal function during the control periods were consistent with the findings of other observers for subjects with congestive heart failure.[20-22,34] The control cardiac indices were low, except in Subject E. B., and effective renal plasma flows (ERPF) were low for all subjects, except E. G. Control venous pressure was increased in all subjects, except in J. M. The control filtration fraction (FF) was elevated in all cases. In those subjects in whom concentrations of urine and serum sodium were determined, control sodium excretion was markedly depressed, except in Subject R. C.

During infusion of the drug, all subjects had an increase in cardiac index and renal blood flow to or toward normal, as illus-

*Table* II

| *Subject and rate of infusion* | *GFR (c.c./min./1.73 M.²)* | | *ERPF (c.c./min./1.73 M.²)* | | *FF (%)* | |
|---|---|---|---|---|---|---|
| | *Mean control* | *Mean isoprot.* | *Mean control* | *Mean isoprot.* | *Mean control* | *Mean isoprot.* |
| R.C. 2γ/min. | 62.6 | 74.1 | 112.5 | 135.7 | 55.7 | 54.7 |
| B.K. 1.8 γ/min. | 40.1 | 44.2 | 69.6 | 111.9 | 58.3 | 39.1 |
| E.D. 1.6 γ/min. | 81.2 | 79.9 | 197.5 | 205.2 | 41.8 | 39.0 |
| J.M. 1.5 γ/min. | 90.7 | 87.0 | 242.5 | 295.6 | 37.5 | 29.4 |
| E.G. 2.4 γ/min. | 149.7 | 141.8 | 612.1 | 642.3 | 24.4 | 22.1 |
| N.K. 1 γ/min. | [60.5 | 57.0 | 126.6 | 132.0 | 24.2 | 21.7 |
| M.B. 1.6 γ/min. | 43.2 | 44.1 | 96.3 | 107.0 | 43.5 | 40.0 |
| E.B. 1.7 γ/min. | 54.9 | 59.2 | 133.0 | 161.2 | 40.8 | 36.3 |
| L.H. 1.3 γ/min. | 50.1 | 44.1 | 85.7 | 101.0 | 57.4 | 41.1 |
| S.N. 4.0 γ/min. | 96.7 | 91.3 | 288.0 | 353.4 | 23.6 | 15.7 |
| J.S. 1.2 γ/min. | 91.0 | 85.5 | 159.5 | 163.3 | 57.8 | 52.5 |
| H.J. 1.4 γ/min. | 72.1 | 100.5 | 241.4 | 359.1 | 29.8 | 27.6 |
| Mean | 74.4 | 75.7 | 197.1 | 230.6 | 41.2 | 34.9 |
| s | 30.5 | 28.7 | 148.1 | 159.6 | 13.7 | 12.0 |
| t | 0.445 | | 3.54 | | 3.76 | |
| p | >.60 | | < .01 | | < .01 | |

GFR: Glomerular filtration rate ($C_{In}$) = $C_{H_2O In} \times \frac{100}{100\text{-Gm. \% plasma protein.}}$

FF: Filtration fraction = $\frac{GFR}{ERPF}$

ERPF: Effective renal plasma flow = $C_{PAH} \times \frac{1}{0.9}$

trated in Fig. 1. A comparison of the increase in cardiac output and renal blood flow demonstrated a proportionately greater rise in cardiac output in 9 of the 12 subjects. Renal blood flow increased in proportion to cardiac output in 2 subjects (B.K. and M.B.), and more than cardiac output in one subject (E.B.). Mean peripheral venous pressure fell significantly in all subjects, whereas mean systemic arterial pressure showed slight and inconsistent changes. Systemic vascular resistance (SVR) and renal vascular resistance (RVR) invariably decreased. SVR decreased proportionately more than RVR for all subjects except B.K. and E.B. This is illustrated in Fig. 2, which demonstrates the relationship of SVR to RVR before and during infusion, and in Table I by the ratio RVR/SVR. Although ERPF increased to or toward normal in all subjects, the effects on glomerular filtration rate (GFR) were slight and variable, as is illustrated in Fig. 3. Five subjects had increased GFR as well as ERPF; however, in only one subject (R.C.) did the GFR

| *Urine flow (c.c./min./M.²)* | | *Na excretion (mEq./min./1.73M.²)* | | *Serum Na (mEq./c.c.)* | | *$C_{Na}/C_{In}$ (%)* | |
|---|---|---|---|---|---|---|---|
| *Mean control* | *Mean isoprot.* | *Mean control* | *Mean isoprot.* | *Mean control* | *Mean isoprot.* | *Mean control* | *Mean isoprot.* |
| 1.05 | 1.08 | 0.224 | 0.349 | 0.126 | 0.130 | 2.84 | 3.62 |
| 0.63 | 1.14 | 0.005 | 0.017 | 0.134 | 0.131 | 0.10 | 0.29 |
| 0.46 | 0.52 | 0.010 | 0.012 | 0.130 | 0.133 | 0.09 | 0.11 |
| 1.46 | 2.47 | 0.099 | 0.118 | 0.137 | 0.138 | 0.80 | 0.98 |
| 2.30 | 1.72 | 0.029 | 0.021 | 0.129 | 0.127 | 0.15 | 0.12 |
| 0.63 | 1.69 | 0.127 | 0.170 | 0.129 | 0.133 | 1.47 | 2.25 |
| 0.30 | 0.36 | 0.023 | 0.028 | 0.142 | 0.138 | 0.37 | 0.46 |
| 0.48 | 0.47 | 0.105 | 0.142 | 0.138 | 0.135 | 1.38 | 1.78 |
| 0.58 | 0.53 | — | — | — | — | — | — |
| 3.02 | 2.94 | — | — | — | — | — | — |
| 2.00 | 5.04 | — | — | — | — | — | — |
| 0.90 | 2.78 | — | — | — | — | — | — |
| 1.15 | 1.73 | 0.078 | 0.107 | 0.133 | 0.133 | 0.90 | 1.20 |
| 0.86 | 1.39 | 0.076 | 0.116 | — | — | 0.75 | 02.1 |
| 1.97 | | 1.93 | | — | | 3.00 | |
| > .05 | | >.20 | | — | | < .02 | |

$\frac{C_{Na}}{C_{In}} \times 100 =$ % filtered Na excreted. $C_{Na}$: Sodium clearance. s = Standard deviation.

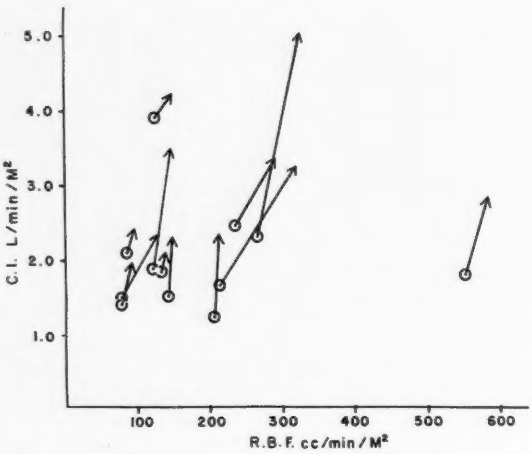

Fig. *1*. See text.

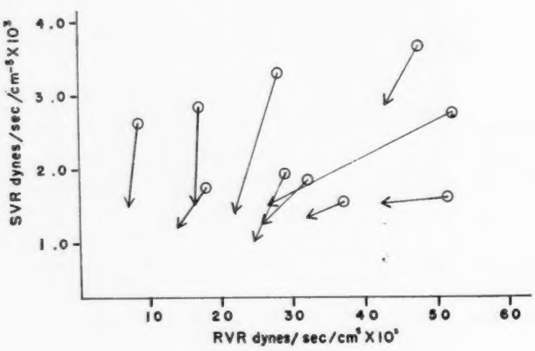

Fig. *2*. See text.

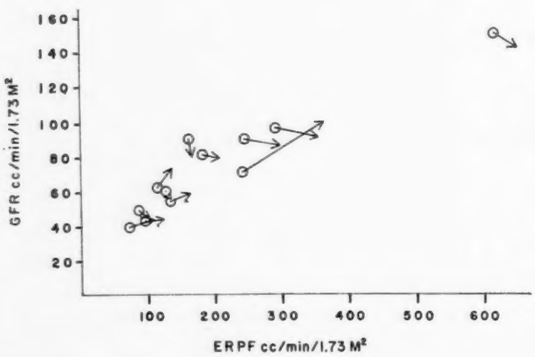

Fig. *3*. See text.

increase to the extent of the ERPF. Accordingly, the FF decreased to normal in 3 subjects and toward normal in the other subjects.

The effects on the flow of urine were variable; 9 subjects showed a comparative increase, and 3 subjects, a decrease in flow. However, the changes in the flow of urine for the group were not statistically significant. Figs. 4 and 5, which relate urine flow (UF) to ERPF and GFR demonstrate that 4 subjects (J.S., N.K., J.M., E.D.) had increases in the flow of urine with increases in ERPF despite relative decreases in GFR.

Concentrations of sodium in the urine were determined before and during infusion of the drug for 8 of the 12 subjects. Figs. 6 and 7 illustrate the relationships of sodium excretion to GFR and ERPF. Four subjects (R.C., B.K., M.B., E.B.) had increases in the excretion of sodium, with associated increases in ERPF and GFR. Three other subjects (N.K., E.D., J.M.) had increased excretion of sodium despite a decrease in GFR. Sodium excretion fell in one subject (E.G.). The effects on the excretion of sodium were not statistically significant, as is shown in Table II. However, when the amounts of filtered sodium per minute were compared to that excreted per minute ($C_{Na}/C_{In}$), a significant increase in the percentage of the filtered sodium which was excreted was noted for the group as a whole, as is also shown in Table II.

## Discussion

In these studies, isoproterenol increased cardiac output and ERPF for all subjects with congestive heart failure, regardless of the type of heart disease, rhythm present (heart block excluded), or state of digitalization. The increased cardiac output was invariably associated with a decrease in systemic and renal vascular resistances. These findings are in contrast to the effects of most other sympathomimetic amines on systemic and renal vascular resistances.[10,13,23-26]

Although RVR was noted to decrease, a comparison of RVR and SVR (expressed as RVR/SVR in Table I) before and during infusion of isoproterenol demonstrated a greater lowering of systemic than of renal vascular resistance in 10 of the 12 subjects studied. The vascular beds which participated in this lowering of systemic vascular resistance were not identified in this study. However, Ahlquist,[6] in studying the effects of isoproterenol in experimental animals, found a slightly greater decrease in vascular resistance in the mesenteric and femoral vascular beds than in the renal vascular bed.

Although ERPF increased and FF de-

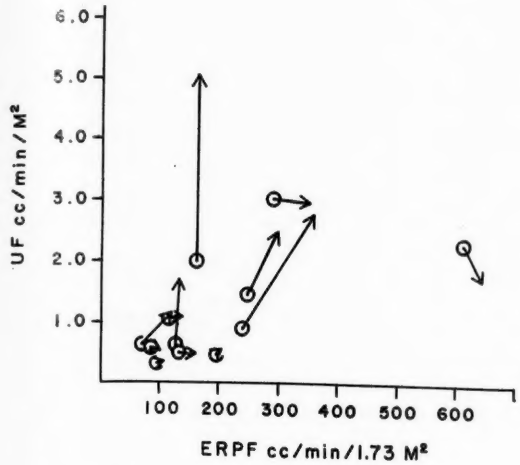


Fig. 4. See text.

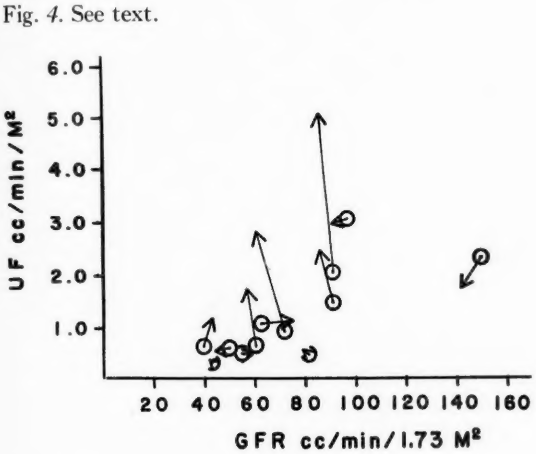


Fig. 5. See text.

creased to or toward normal in all subjects, the effects of isoproterenol on the flow of urine were variable and show no statistically significant change. This may be related to the GFR values, which changed little. However, in the subjects who did show a definite increase or decrease in the flow of urine, this change in the flow of urine was not related to the magnitude or direction of change in GFR. Aviado,[13] using direct intra-arterial injections of isoproterenol, observed increases in RBF and a decreased flow of urine, which he postulated might be due to a relaxant effect of this drug on the smooth muscle of the renal pelvis and ureters. The mechanisms which accounted for a rise in the rate of urine flow in some subjects and a fall or no change in others were not demonstrated in this study.

The increased excretion of sodium that was observed for 7 of 8 subjects is of some interest. Figs. 6 and 7 illustrate that this increased excretion was not related either to an increased GFR or ERPF. Furthermore, changes in the excretion of sodium seemed to be unrelated to changes in the flow of urine. The changes in the excretion of sodium may be related to the increased cardiac output and/or shifts of blood distribution leading to alterations in the hormonal mechanisms concerned with retention of sodium in congestive heart failure.

It has been previously noted[5] that the effects of isoproterenol on cardiac output, heart rate, systemic vascular resistance, oxygen consumption, arterial-venous oxygen difference, and venous pressure are similar to the effects of theophylline in both normal subjects and subjects with congestive heart failure.[27-33] Changes in renal function that were observed during infusion of isoproterenol in this study were also compared with changes in renal function during infusion of theophylline in subjects with congestive heart failure as reported by others.[30,32,33] The effects of

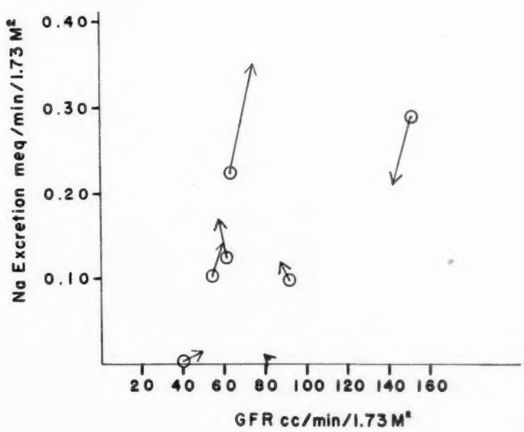


Fig. 6. See text.

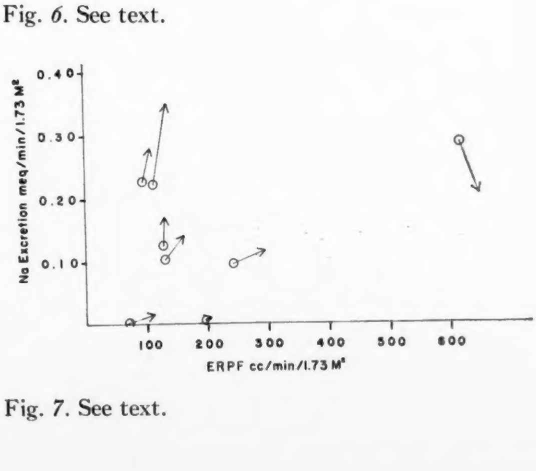


Fig. 7. See text.

these two drugs on GFR are similar. The proportionate rise in RBF and fall in FF observed with isoproterenol are greater than those reported with theophylline. However, the increase in the flow of urine and the excretion of sodium that was reported with theophylline is greater than that observed during administration of isoproterenol in this study.

**Summary**

The cardiovascular-renal effects of isoproterenol were studied in 12 male subjects with congestive heart failure due to heart disease of varied etiologies. Unlike the majority of sympathomimetic amines, isoproterenol increases renal and systemic blood flow and reduces renal and peripheral vascular resistance. Although effective renal plasma flow increased in all subjects, no significant change in glomerular filtration rate, or consistent change in the flow of urine was observed during infusion of isoproterenol. The excretion of filtered sodium during infusion of the drug increased in 7 of 8 subjects.

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# The use of high-speed cinematography in the analysis of cardiovascular motion

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Motion picture photography has been of interest to students of the circulatory system since the beginning of this century. Yandell Henderson[1] observed "ventricular" filling and "valve" movement in a heart model (1905) with his kinetoscope. Subsequently, various aspects of cardiac function have been studied by cinematography, both in this country and abroad. Lutembacher[2] photographed heart sounds, recorded a demonstration of the hepatojugular reflux on film, and used his camera to evaluate the effects of various drugs on the isolated heart of the rabbit at a film speed of 40 cm. per second. Takeuchi[3] and, later, Strughold,[4] using panchromatic film at frame rates of 32 per second, found cinematography useful in evaluating the effects of hypoxia on diastolic volume and stroke output, as did Wiggers[5] in his work on the nature of ventricular fibrillation. Brednow[6] and Landis and associates,[7] as well as Burchell[8] in Visscher's laboratory, used cinecameras at varying frame rates to observe changes in the position and contour of the heart during systole.

World War II brought with it advances in camera design for the analysis of ballistic motion and metal stress, and film speeds of 8,000 to 16,000 frames per second were achieved by devising rotating prism shutters. Prinzmetal and associates[9] pioneered the use of this equipment in medical research during his studies of atrial activation in the atrial arrhythmias, in the Wolff-Parkinson-White syndrome,[10] and in his observations on the effects of experimental coronary artery ligation.[11] However, these earlier high-speed systems had certain disadvantages which limited their usefulness and versatility in animal and clinical research. Contrast, resolution, and over-all film quality were inferior to the more conventional cinecameras. Color photography at high frame rates was difficult, since the "slow" ASA ratings of early color film required intense illumination. The latter could be achieved only through multiple banks of photospot lamps, which produced temperatures high enough to dry or even burn tissue. Finally, there was no provision in such a system to synchronize cardiovascular motion with electrical, sonic, and pressure reference events, although a periscopic optical unit was eventually devised for the purpose of reflecting the stylus and paper of an electrocardiograph upon the film.[10]

The foregoing disadvantages, especially the latter two, have reduced the potential of high-speed cinematography in the analysis and correlation of cardiovascular phenomena. The purpose of the present com-

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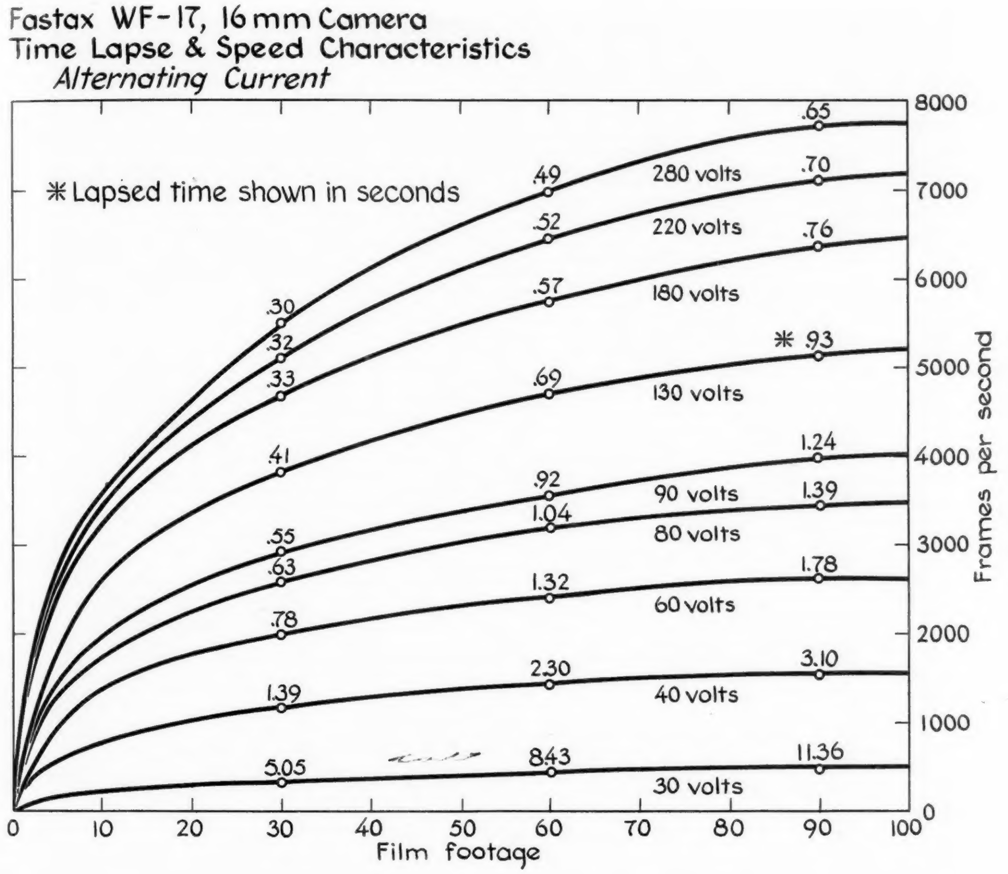


Fig. *1.* The chart indicates the film frame rate and footage-time lapse at increasing AC voltage inputs. Film speeds up to 5,000 frames per second are obtainable with a variable AC transformer, but an additional Goose Control Unit is required for the higher speeds.

munication is to describe a system which surmounts these difficulties and to outline briefly how this system has been applied in certain aspects of circulatory function.

**Method**

The camera is a Wollensak* WF17 16-mm. Fastax utilizing a rotating prism shutter capable of film speeds up to 8,000 pictures per second. Its unique feature is a double-lens system which permits the combined recording of motion picture and oscillographic data. Therefore, any electrical (ECG), mechanical (pressure), or sonic (phonocardiogram) event may be superimposed on the motion picture frames. Fifty-millimeter f/210 Raptar lenses are employed in both motion picture and oscillographic systems, but 63-mm., 75-mm., or longer focal length lenses may be used when additional field detail is desirable.

*Wollensak Optical Co., Rochester, N. Y.

The camera is furnished with two 115-volt AC-DC motors, one to drive and the other to take up the 100-foot roll of film. In the lower speed ranges, power for 350 to 1,500 pictures per second is provided by a 0-30-volt DC rectifier which is controlled by a variable AC transformer. In the intermediate ranges up to 5,000 pictures per second a variable AC transformer, 0-135 volts, is employed. For maximum film speeds, a Goose Control Unit is required. This unit incorporates an AC autotransformer with a maximal output of 280 volts. The unit allows for synchronization of the camera with the event under study and provides a time delay mechanism which regulates sprocket starting torque, in order to avoid damage to the film perforations when the voltages required for the highest film speeds are applied. Time lapse and speed characteristics at various AC inputs are shown in Fig. 1. The precise film speed at any

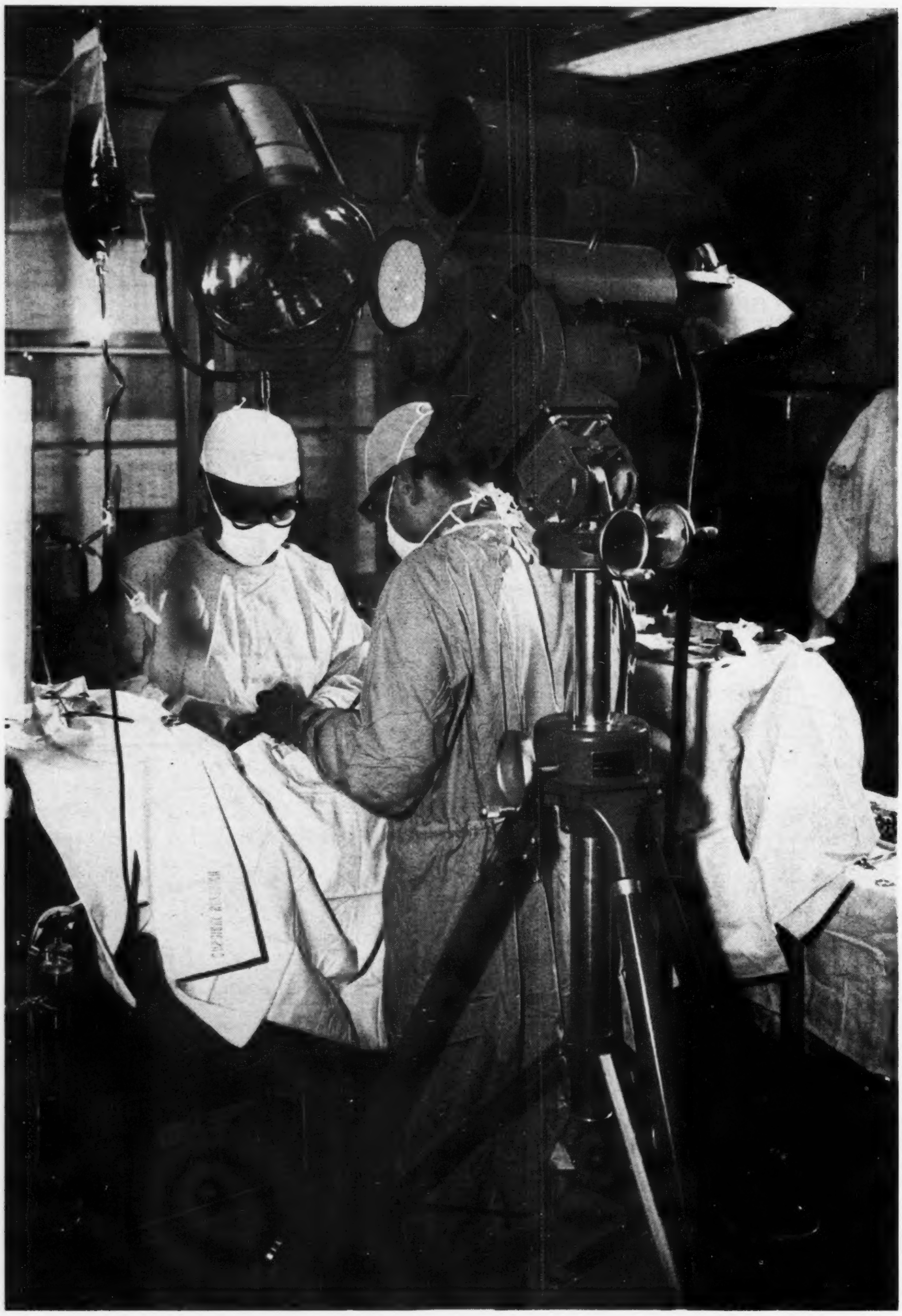

Fig. *2*. Photograph of camera to show oscilloscope tube mounted atop camera body just above the oscillographic lens, which is set in the door of the film magazine. The metal assembly, which holds two plane mirrors mounted opposite each other at 45-degree angles, is retracted. The high-intensity Xenon lamp stands opposite the camera.

moment is provided by a timing light which makes 120 pips, or marks, per second between sprocket holes when energized by a 60-cycle current. The light can also inscribe 100 or 1,000 pips per second when activated by a timing light generator.

The oscillographic lens is mounted on the camera door at right angles to the motion picture lens. Laboratory and operating room conditions require that the oscilloscope face, and its lens be aligned and in proper focus for, any camera eleva-

tion and tilt angle. This has been accomplished in the following manner. The cathode-ray tube of a Tektronix dual-beam oscilloscope, Type 502,* was removed and mounted separately in a metal housing atop the camera body. The face of the cathode-ray tube is situated just above and in the same plane as the camera door (Fig. 2). The circuitry and controls of the oscilloscope are mounted on a metal shelf at the base of the camera tripod, and, for simplicity, the power supplies of the tube and camera are combined in a single cable which runs from the face of the oscilloscope control panel to the undersurface of the housing of the cathode-ray tube. Two plane mirrors which are set at angles of 45 degrees in the same vertical plane reflect the cathode-tube image into the oscilloscope lens through an angle of 180

*Tektronix, Inc., Portland, Ore.

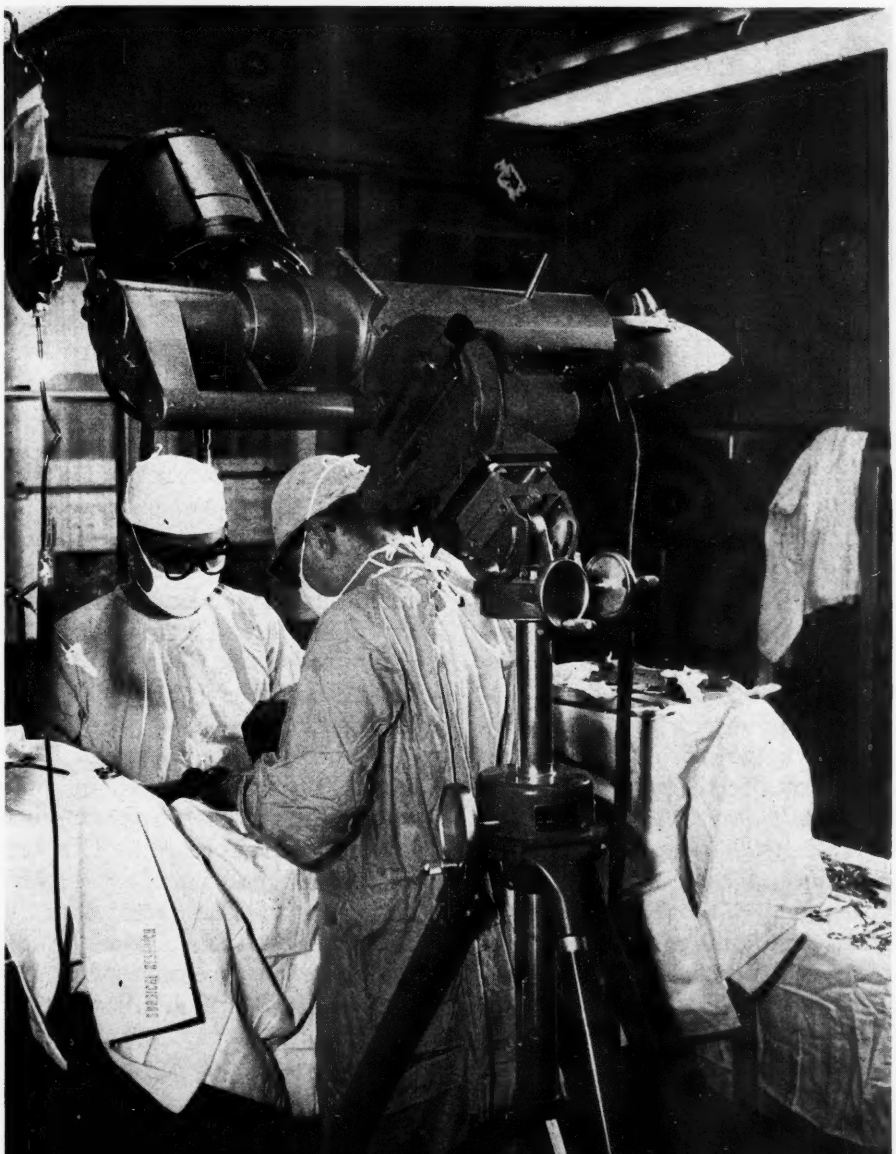

Fig. 3. The metal assembly is in position for recording, and the oscilloscope beams are reflected through an angle of 180 degrees into the oscillographic lens. The two mirrors are opposite each other at the bends of the "C"-shaped housing.

*Table* I. *Illumination characteristics of Xenon quartz lamp: lamp to subject distance of 3 feet*

| *Lamp output (kilowatts)* | *Filter* | *Full spot* | |
|---|---|---|---|
| | | *Area covered* | *Foot-candles* |
| 2.5 | Clear | 3-inch diameter | 120,000 |
| 5.0 | Clear | 3-inch diameter | 240,000 |
| 7.5 | Clear | 3-inch diameter | 480,000 |
| 2.5 | Medium | 7-inch diameter | 35,000 |
| 5.0 | Medium | 7-inch diameter | 70,000 |
| 7.5 | Medium | 7-inch diameter | 140,000 |
| 2.5 | Maximum density | 10-inch diameter | 15,000 |
| 5.0 | Maximum density | 10-inch diameter | 30,000 |
| 7.5 | Maximum density | 10-inch diameter | 60,000 |

degrees. The mirrors are set at the right-angle joints of a tubular metal assembly which has the shape of a reversed "C". The inner surfaces of the metal are blackened to absorb stray light. This metal assembly is hinged to the front of the housing of the cathode-ray tube and is readily swung in and out of position. Fig. 3 shows the entire assembly in position for recording.

The Tektronix dual-beam oscilloscope is ideally suited for photographic purposes. Its sensitivity, permitting gains up to 200 microvolts per centimeter, makes it unnecessary to employ additional preamplifiers for electrocardiography and phonocardiography, thus simplifying the instrumentation. It is fitted with a P-11 blue phosphor of short persistence and high intensity adequate for the purposes of high-speed cinematography. During recording the horizontal time sweep of both beams is suspended. The phosphorescent dots move only vertically, and the film movement acts as the horizontal time base.

Illumination is provided by a single, high-intensity WF-360 Xenon lamp.* The lamp bulb is quartz. The source size is approximately 5 mm. in diameter and has a color temperature of 5,700°K. The illumination characteristics of the lamp are shown in Table I. The control unit is cased in a portable console. The voltage striking circuit makes use of a 25-kilovolt repeating pulse at a current flow of 25 amperes. The lamp simmers at 700 watts, and one of three power levels may be selected, each with its own period limiting circuit. At 2.5 kilowatts the pulse is of 10-second duration, at 5.0 kilowatts it is of 5-second duration, and at 7.5 kilowatts the duration is 2 seconds. Power for the unit is furnished by a 42-volt supply from seven 6-volt wet batteries. Silicon rectifiers may also be used as the power supply. The output of heat is low, so that no discomfort is felt on the face if the lamp is brought to a maximum spot at a distance of 3 feet and pulsed at 7.5 kilowatts. This provides an illumination of 140,000 foot-candles with a medium filter, and 480,000 foot-candles with a clear filter.

The color temperature of 5,700°K makes possible the use of daylight film. For color photography, both Superanscochrome and commercial Ektachrome ER, perforated for high-speed photography, have been very satisfactory. The latter film is currently preferred because it is less grainy.

Motion picture analysis is facilitated by a projector* which allows the choice of viewing at 16 pictures per second, 2 pictures per second frame-by-frame advance, or still projection. It also incorporates a frame counter. In this manner the film speed at any time can be determined from the timing-light pips, and the oscillographic and motion picture events may be temporally correlated. It has also been useful in still presentation of motion picture

*Wollensak Optical Co., Rochester, N. Y.

*Wollensak Optical Co., Rochester, N. Y.

data to trace silhouettes from representative projected frames during different parts of the cardiac cycle and to superimpose them in a composite drawing.

## Discussion

The present system of high-speed cinematography incorporates a number of recent advances in instrumentation and technique and has particular application to the study of cardiovascular phenomena. In addition to the unique motion picture and oscillographic dual-lens systems, improved prism-shutter design and viewfinder units have enhanced resolution and over-all film quality at high frame rates. The availability of a high-intensity, cool quartz lamp has greatly simplified lighting problems. Illumination is provided by a single lamp, replacing the banks of 12 or more photospot lights which were previously required. Drying or burning of tissues is not noted at full spot when a medium filter is used, or at flood when the filter is clear.

The addition of an oscillographic lens permits the combined recording of cardiovascular motion, sounds, pressures, and the electrocardiogram. This has expanded the scope of cinematography as a method for analyzing circulatory events, and it has been useful both in animal research and in clinical investigation.

We have used the technique in the surgical laboratory to study the sequence of right ventricular contraction, the effects of ventriculotomy on the contraction of the right ventricle, and the behavior of outflow-tract patches. In these studies, to be fully reported elsewhere,[12,13] high-speed cinematography with simultaneous electrocardiography and phonocardiography was useful in establishing the asynchronous character of right ventricular contraction and in analyzing the adverse effects of vertical ventriculotomy on the pattern of right ventricular motion.

The method is also suitable for the study of externally recordable circulatory events, such as cardiac impacts on the chest wall, and arterial and venous pulsations. For example, in a case of carcinoid syndrome with tricuspid insufficiency, motion analysis disclosed the bifid character of the systolic jugular pulsations. A second peak appeared 10 milliseconds after the initial impact and 27 milliseconds after the Q wave of the electrocardiogram, suggesting a venous bisferiens phenomenon.

In conclusion, the method is particularly suitable for the analysis of complex intrinsic movements of the heart and great vessels as viewed from the surface of the heart. However, photography of the heart does require extensive thoracotomy and pericardial resection, which limits the validity of observations in regard to rotational movements, and since the distance from the heart to the lens may not remain constant throughout the cardiac cycle, apparent changes in heart volume cannot be directly interpreted.

Finally, it is important to select a camera speed appropriate to the event under study, since excessive film speeds may obscure slow displacements, just as the details of rapid motion are lost at frame rates which are too slow. Thus, the jugular bisferiens pulse in tricuspid insufficiency was well recorded at 240 pictures per second, whereas the details of motion in the outflow tract of the right ventricle were best studied at 800 to 1,200 pictures per second.

## Summary

1. A method of high-speed cinematography for the study of cardiovascular motion has been described.

2. Its unique feature is a dual-lens system which enables the simultaneous recording of motion picture and oscillographic frames. This innovation allows for the appearance of electrocardiogram, sounds, and pressures on the particular aspect of cardiovascular motion under study, and makes possible the use of the camera for the precise measurement of circulatory events.

3. The present method also incorporates recent improvements in high-speed shutter systems, focusing devices, frame speed timers, and light sources. In particular, the utilization of a high-intensity light source with low output of heat has avoided tissue damage and increased the applicability of the unit.

4. The application of the method both to the experimental laboratory and to clinical research is briefly described.

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# Acute effects of intravenous chlorothiazide upon cardiovascular hemodynamics

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The mechanisms of action of chlorothiazide in reducing blood pressure have not been definitively established. Various possibilities have been proposed. These include: (1) decrease in total circulating plasma volume secondary to the diuretic effects of this agent, resulting in diminished cardiac filling, and, thereby, in reduced cardiac output; (2) changes in extracellular and intracellular electrolyte relationships, resulting in decreased arteriolar tone or dehydration of "waterlogged" arterioles, hemodynamically reflected as diminished total peripheral resistance; (3) vasodilation by direct effect upon peripheral vessels or upon the central nervous system; (4) decreased responsiveness to endogenous vasopressor mechanisms. The present study, which concerns the acute effects of the intravenous administration of chlorothiazide upon cardiovascular dynamics in hypertensive and normotensive subjects, was performed in order to gain more information about the mechanisms of action of this drug.

An important property of chlorothiazide is a limitation of the hypotensive effect to the hypertensive state. Therefore, it appeared that an investigation of this type could also serve to study the properties of the circulatory system in patients with hypertension, especially as it differs from the normal state.

## Method

Twelve patients, 5 women and 7 men, were the subjects of this study (Tables I and II). They ranged in age from 32 to 65 years. Ten patients (Patients 1-10) had persistent systemic arterial hypertension as defined by systolic pressures greater than 140 mm. Hg and diastolic pressures greater than 90 mm. Hg (except Patient 6, in whom the control pressures averaged 187/75 mm. Hg). Two patients (Patients 11, 12) were normotensive. Specific antihypertensive drugs and diuretics were avoided for several weeks prior to the study. Further information concerning associated diseases, the presence of heart failure, and ancillary cardiac therapy are tabulated in Table I.

The patients were hospitalized for at least 1 to 2 weeks. During this period, routine clinical observations were made and pertinent laboratory data obtained. Fluid balances were evaluated according to daily fasting weights, daily outputs of urine, and frequent determinations of serum electrolytes, and, in some patients, of urine electrolytes.

The acute effects of intravenous chloro-

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thiazide upon cardiovascular hemodynamics were then studied. The patients were in the resting recumbent positions and were not given premedication. The standard technique of right heart catheterization was performed in 10 cases (Patients 1, 4-12). In one case (Patient 2) systemic arterial pressures (direct), cardiac outputs (indicator-dilution method), and heart rates were measured directly. In Patient 3, only systemic arterial pressures (direct) and heart rates were measured. Control data were obtained initially. Cardiac outputs were measured by the indicator-dilution method according to Hamilton and co-workers.[1-3] Known amounts of dye (Cardio-green) were injected rapidly into the pulmonary artery (Patients 1, 4-7, 9-12) or right atrium (Patient 8) through the catheter or into an antecubital vein (Patient 2) through an indwelling arterial needle (Cournand) and time-concentration curves of dye were obtained from the peripheral (brachial) artery by means of a cuvette densitometer in conjunction with a constant-flow system.* The volume of blood between the point of injection and the site of sampling (including all temporally related sites) was calculated as the product of cardiac output and mean circulation time (central blood volume).[4,5] Pressures were obtained with Statham strain-gauge transducers and recorded on a multichannel oscillographic photographic recorder. Mean pressures were obtained by electrical integration of the pressure pulses. The point of zero reference for measurements of intracardiac pressures was taken at 5 cm. below the angle of Louis. Total pulmonary vascular, pulmonary "arteriolar," and total peripheral resistances were calculated according to standard formulas (Poiseuille). Resistance is expressed as dynes per second per cm.$^{-5}$ by the use of conversion factors.†

Since the parameters measured did not vary significantly during control periods, only average values are tabulated (Tables I and II).

After the control data were obtained, chlorothiazide, 0.75 to 1.00 Gm. in isotonic solution, was administered intravenously over a period of 5 to 10 minutes. Measurements were then made during the following 140 to 175 minutes. This latter period will henceforth be referred to as the *immediate postdrug phase*. Pressures and heart rates were measured frequently. Cardiac outputs were determined 3 to 6 times by the indicator-dilution method, beginning 5 to 25 minutes (average 16 minutes) to 70 to 170 minutes (average 138 minutes) after administration of the drug. Vascular resistances, stroke volumes, and central blood volumes were calculated from these data.

The following were measured frequently during the control periods and during the immediate postdrug phases: peripheral arterial hematocrits (Patients 1, 3, 5-12), and outputs of urine and intakes of fluid (Patients 1, 3, 4, 6, 8-12) (subjects undergoing cardiac catheterization received a constant infusion of 5 per cent glucose). The following were measured at least once during the control periods and at approximately 100 to 150 minutes after administration of the drug: total plasma volume ($I^{131}$-labeled human serum albumin method), converted to total blood volume by the use of peripheral hematocrits (volumes during the second periods were measured 10 to 15 minutes after the administration of additional radioactive material) (Patients 1, 8, 10), ventilations, oxygen consumptions, and respiratory quotients (analysis* of expired air collected in a Tissot spirometer during 3 minutes of quiet breathing) (Patients 2-12), and systemic arterial oxygen saturations[7] (Patients 5, 7, 8, 10-12).

Changes in cardiovascular hemodynamics were evaluated in terms of statistical probabilities. In order to determine whether changes are due to chance variations per se, or to the action of an introduced variable (chlorothiazide in this study), 29 consecutive right heart catheterizations performed in this laboratory in adults with varied types of heart disease were analyzed. In each of these studies at least two control "resting" cardiac outputs (indicator-dilution method) and multiple pressures were measured and resistances calculated at intervals of 22 to 143 minutes

*Gilford Model 103 cuvette densitometer and Gilford Model 105-S constant-flow system.

†1.332, conversion factor from mm. Hg to dynes per cm.$^{-5}$

*Scholander gas analyzer.[6]

(average 41 minutes) while the patients' states were considered to be constant. Mean values, standard deviations, and 95 per cent confidence limits for the various measures of cardiovascular dynamics were established in order to define the statistical ranges for chance variations between two or more measurements. A wide range of abnormalities in cardiodynamics was present in this control group, as would be expected in any series of patients with heart disease. It was thought, therefore, that greater reliability in an evaluation of significance would exist if the confidence limits were expressed in terms of percentage differences rather than differences in absolute values. Two exceptions are pulmonary "wedge" and right ventricular end-diastolic pressures. These parameters are expressed in terms of absolute changes because (1) only minimal variations usually occur during a "resting" state, and (2) small variations in their usually low numerical values frequently result in inordinately high percentage changes.

Changes in cardiovascular dynamics in the present series of 12 patients who received chlorothiazide are evaluated in terms of statistical significance at the 5 per cent level based upon the confidence limits as determined from the control group (*vide supra*). Changes which are considered to be statistically significant are appropriately indicated in Tables I and II and in the description of the results. In the latter section, maximal percentile changes in the various parameters are indicated in parentheses, whereas broader statements are made concerning durations of over-all significant changes. The patients are divided into two groups: those in whom chlorothiazide induced systemic arterial hypotension during the immediate postdrug phases (Group A), and those in whom the systemic blood pressures did not change during these periods (Group B).

## Results

*Group A. Subjects in whom chlorothiazide induced systemic arterial hypotension during the immediate postdrug phases* (*Patients 1-7*) (*Tables I and II*). In 7 patients (Nos. 1-7), significant declines in systolic (average −33 per cent), diastolic (average −31 per cent), and mean (average −34 per cent) systemic arterial pressures occurred during the immediate postdrug phases. These 7 patients had pre-existing hypertension. In 3 subjects (Nos. 2, 6, 7), hypotension occurred 20, 66, and 50 minutes, respectively, after chlorothiazide had been administered, and lasted an average of 29 minutes. In the other 4 subjects (Nos. 1, 3-5), hypotension appeared 26 to 110 minutes (average 62 minutes) after the drug was administered and persisted throughout the remainder of the immediate postdrug phases. In 4 (Nos. 1, 4-6) of these 7 subjects, significant decreases in cardiac outputs (average −34 per cent) occurred concomitant with the declines in blood pressures. The decreases in cardiac outputs were associated with significant reductions in stroke volumes (average −31 per cent) and in central blood volumes (average −26 per cent).

Total peripheral resistances declined significantly (average −30 per cent) in 3 subjects (Nos. 1, 2, 7) and increased significantly (average +25 per cent) in 3 others (Nos. 4-6) concomitant with the reductions in systemic arterial pressures. It is of interest that in the latter 3 patients the extent of declines in cardiac outputs were greater (−34 to −47 per cent) than in the former 3 patients (−19, −27, and +15 per cent). This will be commented upon later.

In Patient 1, control pressures in the lesser circulation were normal and did not change after chlorothiazide had been administered. In 4 subjects (Nos. 4-7), moderate degrees of pulmonary hypertension were present in the control periods. In these patients, pulmonary arterial pressures decreased to, or almost to, normal during the immediate postdrug phases. In 3 patients (Nos. 4-6), control right ventricular end-diastolic pressures were moderately elevated. In 2 patients (Nos. 4, 6), significant declines occurred during the immediate postdrug phases. Control pulmonary "wedge" pressures were elevated in 2 patients (Nos. 5, 6) in whom they were measured. Significant reductions were noted in both patients after the drug was administered. There were no changes in pulmonary "arteriolar" resistances.

There were no significant changes in the following parameters in those subjects in

*Table I. Cardiovascular hemodynamics before and after administration of chlorothiazide*

| Patient number, sex, age (yr.) | Clinical status | | Pressure (mm. Hg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Peripheral artery | | | | Pulmonary artery | | | |
| | | | S | D | M | T | S | D | M | T |
| 1. F, 32 | Diabetes, chronic nephritis, | I | 180 | 111 | 140 | | 21 | 9 | 14 | |
| | mild azotemia. Therapy: | II | 107 | 76 | 86 | 76 | 25 | 10 | 16 | |
| | salt intake unlimited; | Diff. | −41 | −32 | −39 | (45-140E) | +16 | +10 | +12 | |
| | insulin | | | | | | | | | |
| 2. M, 35 | Therapy: salt intake | I | 184 | 110 | 143 | | | | | |
| | unlimited | II | 91 | 48 | 63 | 35 | | | | |
| | | Diff. | −51 | −56 | −56 | (20-35) | | | | |
| 3. F, 48 | Therapy: salt intake | I | 162 | 91 | 114 | | | | | |
| | unlimited | II | 96 | 60 | 79 | 95 | | | | |
| | | Diff. | −41 | −34 | −31 | (26-175E) | | | | |
| 4. M, 61 | LHD, RHD. Therapy: | I | 254 | 110 | 155 | | 50 | 18 | 29 | |
| | digoxin; salt intake, | II | 204 | 86 | 123 | 150 | 24 | 8 | 13 | 175 |
| | 1.0-1.5 Gm. daily | Diff. | −20 | −22 | −21 | (110-175E) | −52 | −56 | −55 | (25-130E) |
| 5. F, 49 | MS. LHD, RHD. Therapy: | I | 187 | 102 | 130 | | 41 | 22 | 29 | |
| | digoxin; salt intake, | II | 154 | 87 | 118 | 170 | 28 | 14 | 20 | 130 |
| | 4.0-5.0 Gm. daily | Diff. | −18 | −15 | −9 | (65-170E) | −32 | −36 | −31 | (25-130E) |
| 6. F, 65 | Coronary artery disease. | I | 187 | 75 | 107 | | 43 | 17 | 24 | |
| | LHD, RHD. Therapy: | II | 157 | 63 | 91 | 115 | 33 | 15 | 21 | 170 |
| | digoxin; salt intake, | Diff. | −16 | −16 | −15 | (66-115) | −23 | −12 | −13 | (110-170E) |
| | 1.0-1.5 Gm. daily | | | | | | | | | |
| 7. M, 48 | LHD. Therapy: salt | I | 189 | 132 | 156 | | 43 | 21 | 25 | |
| | intake, 4.0-5.0 Gm. | II | 111 | 81 | 92 | 50 | 18 | 6 | 12 | 66 |
| | daily | Diff. | −41 | −39 | −41 | (50-73) | −58 | −71 | −52 | (25-145E) |
| 8. M, 48 | Therapy: salt intake | I | 217 | 127 | 154 | | | | | |
| | unlimited | II | 212 | 119 | 146 | | | | | |
| | | Diff. | −2 | −6 | −5 | | | | | |
| 9. M, 41 | MI, MS. LHD, RHD. | I | 143 | 100 | 113 | | 67 | 40 | 50 | |
| | Therapy: digoxin; salt | II | 135 | 87 | 108 | | 58 | 36 | 45 | |
| | intake, 1.0-1.5 Gm. daily | Diff. | −6 | −13 | −4 | | −13 | −10 | −10 | |
| 10. F, 62 | Chronic nephritis. LHD, | I | 231 | 107 | 158 | | 73 | 27 | 44 | |
| | RHD. Therapy: digitalis; | II | 221 | 103 | 147 | | 64 | 24 | 41 | |
| | salt intake, 4.0-5.0 Gm. | Diff. | −4 | −4 | −7 | | −12 | −11 | −7 | |
| | daily | | | | | | | | | |
| 11. M, 51 | LHD. Therapy: salt | I | 123 | 66 | 85 | | 31 | 10 | 17 | |
| | intake unlimited | II | 116 | 64 | 76 | | 25 | 9 | 14 | |
| | | Diff. | −6 | −3 | −11 | | −19 | −10 | −18 | |
| 12. M, 37 | MI, MS, AS. LHD, RHD. | I | 121 | 74 | 94 | | 105 | 46 | 62 | |
| | Therapy: digitalis; salt | II | 112 | 68 | 86 | | 94 | 42 | 59 | |
| | intake, 1.0-1.5 Gm. daily | Diff. | −7 | −8 | −9 | | −10 | −9 | −5 | |

For footnotes see Table II.

| | | | | *Resistance (dynes sec. cm.$^{-5}$)* | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *Pulmonary* "wedge"* | | *Right* ventricular* | | *Total systemic* | | *Total pulmonary vascular* | | *Pulmonary "arteriolar"* | |
| *M* | *T* | *D* | *T* | | *T* | | *T* | | *T* |
| 6 | | 6 | | 2,300 | | 260 | | 100 | |
| | | 5 | | 1,760 | 35 | 200 | | | |
| | | −1 | | −23 | (15-75E) | −23 | | | |
| | | | | 2,750 | | | | | |
| | | | | 2,200 | 20 (20) | | | | |
| | | | | −20 | | | | | |
| | | 6 | | 2,930 | | 630 | | 200 | |
| | | 0 | 170 | 3,480 | 170 | 370 | | | |
| | | −6 | (60-170E) | +16 | (170E) | −41 | | | |
| 22 | | 6 | | 2,450 | | 520 | | 195 | |
| 14 | 58-65 | 4 | | 3,400 | 120 | 720 | | 270 | |
| −8 | | −2 | | +28 | (25-120E) | +28 | | +28 | |
| 12 | | 10 | | 3,000 | | 720 | | 470 | |
| 9 | 90, 170 | 7 | 120 | 4,400 | 110 | 950 | | 410 | |
| −3 | | −3 | (120-170E) | +32 | (25-150E) | +24 | | −13 | |
| | | 4 | | 5,000 | | 730 | | | |
| | | 3 | | 2,700 | 60 | 310 | 60 | | |
| | | −1 | | −46 | (60-73) | −58 | (60-73) | | |
| | | 1† | | 2,160 | | | | | |
| | | 0 | | 2,490 | | | | | |
| | | −1 | | +13 | | | | | |
| 29 | | 18 | | 3,660 | | 1,770 | | 660 | |
| 23 | 60, 120 | 15 | 60 | 2,560 | 105 | 1,100 | 170 | 525 | |
| −6 | | −3 | (60-65) | −30 | (25-150E) | −38 | (160-170E) | −21 | |
| | | 6 | | 3,300 | | | | | |
| | | 4 | | 2,800 | | | | | |
| | | −2 | | −15 | | | | | |
| 2 | | 3 | | 2,540 | | 440 | | 320 | |
| 3 | | 0 | 45 | 2,040 | | 360 | | 360 | |
| +1 | | −3 | (45-97E) | −19 | | −18 | | +11 | |
| 34 | | 6 | | 2,030 | | 1,310 | | 700 | |
| 32 | | 4 | | 2,300 | | 1,650 | | 770 | |
| −2 | | −2 | | +12 | | +20 | | +9 | |

*Table* II. *Cardiovascular hemodynamics and outputs of urine before and after administration of*

| *Patient* | | *$O_2$ consumption (c.c./min./M.$^2$)* | | *Cardiac index (L./min./M.$^2$)* | | *Heart rate (beats/min.)* | | *Stroke volume (c.c./beat)* | |
|---|---|---|---|---|---|---|---|---|---|
| | | | *T* | | *T* | | *T* | | *T* |
| 1. | I | 101 | | 2.99 | | 103 | | 49 | |
| | II | | | 2.43 | 75 (75E) | 92 | | 40 | 75 (75E) |
| | Diff. | | | −19 | | −11 | | −18 | |
| 2. | I | 136 | | 2.10 | | 78 | | 52 | |
| | II | 137 | | 1.54 | 140 (140E) | 73 | | 40 | 140 (140E) |
| | Diff. | +1 | | −27 | | −6 | | −23 | |
| 3. | I | 93 | | | | 75 | | | |
| | II | 71 | 120 | | | 60 | 35 (35-170E) | | |
| | Diff. | −24 | | | | −20 | | | |
| 4. | I | 118 | | 2.40 | | 57 | | 73 | |
| | II | 138 | 100 | 1.59 | 170 (140-170E) | 64 | | 51 | 170 (140-170E) |
| | Diff. | +14 | | −34 | | +11 | | −30 | |
| 5. | I | 181 | | 2.40 | | 95 | | 44 | |
| | II | 176 | | 1.27 | 130 (65-130E) | 105 | | 22 | 130 (30-130E) |
| | Diff. | −3 | | −47 | | +10 | | −50 | |
| 6. | I | 114 | | 1.69 | | 78 | | 37 | |
| | II | 109 | | 1.09 | 110 (50-110) | 73 | | 25 | 110 (50-110) |
| | Diff. | −4 | | −35 | | −6 | | −32 | |
| 7. | I | 142 | | 1.15 | | 100 | | 24 | |
| | II | 123 | | 1.35 | | 85 | 80 (80) | 31 | 80 (80) |
| | Diff. | −13 | | +15 | | −15 | | +23 | |
| 8. | I | 117 | | 2.76 | | 87 | | 65 | |
| | II | 124 | | 2.30 | | 100 | | 55 | |
| | Diff. | +6 | | −17 | | +13 | | −15 | |
| 9. | I | 178 | | 1.25 | | 112 | | 21 | |
| | II | 169 | | 1.77 | 45 (45-150E) | 103 | | 33 | 105 (25-150E) |
| | Diff. | −5 | | +29 | | −8 | | +36 | |
| 10. | I | 117 | | 2.58 | | 105 | | 38 | |
| | II | 113 | | 2.26 | | 97 | | 34 | |
| | Diff. | −3 | | −12 | | −8 | | −11 | |
| 11. | I | 125 | | 1.52 | | 60 | | 46 | |
| | II | 137 | | 1.83 | | 65 | | 50 | |
| | Diff. | +9 | | +16 | | +8 | | +8 | |
| 12. | I | 152 | | 2.23 | | 110 | | 33 | |
| | II | 147 | | 1.84 | | 124 | 105 (105-135E) | 25 | 125 (125) |
| | Diff. | −10 | | −17 | | +13 | | −24 | |

Footnotes for Tables I and II:
*Differences between I and II are given as absolute values.
†Right atrial mean pressure.
S: Systolic. D: Diastolic. M: Mean. E: Final measurement for the acute study. LHD: Left heart decompensation. RHD: Right heart
periods. II: Cardiovascular hemodynamics during the immediate postdrug phases. Values which are maximally different from those
indicate the times after drug administration when the maximal differences between I and II were present; numbers within parentheses
maximum. The appropriate space is left blank if no significant changes occurred. Outputs of urine indicate total amounts during each

*chlorothiazide*

| *Central blood volume* | | *Hematocrit* | | *Systemic artery $O_2$ saturation* | | *TPV* | *TBV* | *Urine output* |
|---|---|---|---|---|---|---|---|---|
| (*c.c.*) | *T* | (%) | *T* | (%) | *T* | (*c.c.*) | (*c.c.*) | (*c.c.*) |
| 1,075 | | 26 | | 96 | | 2,210 | 3,100 | 50 |
| 820 | 75 (75E) | 26 | | | | 2,260 | 3,060 | 120 |
| −24 | | 0 | | | | +2 | −1 | |
| 1,450 | | | | | | | | |
| 1,100 | 140 (140E) | | | | | | | |
| −24 | | | | | | | | |
| | | 30 | | | | | | 40 |
| | | 31 | | | | | | 500 |
| | | +3 | | | | | | |
| 1,400 | | | | 93 | | | | 750 |
| 1,070 | 170 (140-170E) | | | | | | | 750 |
| −24 | | | | | | | | |
| 1,200 | | 40 | | 94 | | | | |
| 810 | 130 (130E) | 40 | | 91 | | | | |
| −32 | | 0 | | −3 | | | | |
| 860 | | 42 | | | | 4,370 | 7,800 | 150 |
| 630 | 50 (50-110) | 40, 44 | | | | | | 560 |
| −27 | | −5, +5 | | | | | | |
| 1,640 | | 43 | | 89 | | | | |
| 1,660 | | 42 | | 93 | | | | |
| +1 | | −2 | | +4 | | | | |
| 940 | | 40 | | 94 | | 2,820 | 4,700 | 50 |
| 870 | | 39 | | 96 | | 2,940 | 4,800 | 500 |
| −7 | | −3 | | +2 | | +4 | +2 | |
| 1,430 | | 51 | | 95 | | | | 50 |
| 1,900 | 105 (25-150E) | 52 | | | | | | 475 |
| +25 | | +2 | | | | | | |
| 1,400 | | 42 | | 83 | | 2,430 | 4,200 | 70 |
| 1,240 | | 42 | | 83 | | 2,420 | 4,200 | 200 |
| −11 | | 0 | | 0 | | 0 | 0 | |
| 1,275 | | 42 | | 94 | | 3,150 | 5,420 | 70 |
| 1,600 | | 43 | | 95 | | | | 140 |
| +20 | | +2 | | +1 | | | | |
| 1,790 | | 30 | | 91 | | 3,620 | 5,260 | 100 |
| 1,470 | | 31 | | 90 | | | | 265 |
| −18 | | +3 | | −1 | | | | |

decompensation. MS: Mitral stenosis. MI: Mitral insufficiency. AS: Aortic stenosis. I: Cardiovascular hemodynamics during control
of the control periods are tabulated. Diff. denotes per cent differences between I and II. In columns *T*, numbers outside parentheses
indicate times during which over-all significant changes were present. The latter includes changes which are significant but less than
period. TPV: Total plasma volume. TBV: Total blood volume.

whom they were measured in the control periods and during the immediate postdrug phases: systemic arterial hematocrits, systemic arterial oxygen saturations, respiratory quotients, ventilations, oxygen consumptions, and total plasma and total blood volumes.

Outputs of urine and intakes of fluid were measured in 4 subjects (Nos. 1, 3, 4, 6) during the control and immediate postdrug phases. Three of these patients (Nos. 1, 4, 6) received 450 to 500 c.c. of isotonic glucose intravenously at a constant rate during the entire study. In Patients 1, 3, and 6, outputs of urine increased by 70 to 450 c.c. (average, 307 c.c.) during the immediate postdrug phases as compared to control periods, and in Patient 4, no increase in the output of urine occurred. In Patients 3, 4, and 6, the total outputs of urine exceeded the intakes of fluid by 200 to 950 c.c. (average 567 c.c.), whereas in Patient 1 the intake of fluid exceeded the output of urine by 330 c.c. In Patients 3, 6, and 7, concentrations of sodium, chloride, and potassium in the urine increased twofold in the immediate postdrug phases as compared to control periods.

*Group B. Subjects in whom no changes in systemic arterial pressures occurred during the immediate postdrug phases* (*Patients 8-12*) (*Tables I and II*). In 5 subjects (Nos. 8-12), no changes in systemic arterial blood pressures occurred during the immediate postdrug phases. Three of these patients (Nos. 8-10) had pre-existing hypertension and 2 (Nos. 11, 12) were normotensive. In one case (Patient 9), significant increases in cardiac outputs and reductions in total peripheral resistances occurred from 45 to 150 (the last determination) minutes after the drug was administered. Stroke volumes and central blood volumes were increased at the same time.

In 3 patients (Nos. 9-12), pulmonary arterial pressures were elevated to varying degrees during the control periods. No changes occurred after chlorothiazide had been given. In Patients 9 and 12, control pulmonary "wedge" and right ventricular end-diastolic pressures were considerably elevated. In Patient 9, significant reductions occurred in these pressures after the drug had been given, whereas there were no changes in Patient 12. In Patients 10 and 11, control right ventricular end-diastolic pressures were normal. In Patient 10, no changes were noted during the drug period, whereas a slight decrease occurred in Patient 11.

There were no changes in pulmonary "arteriolar" resistances.

There were no significant changes in the following parameters in those subjects in whom they were measured in the control periods and during the immediate postdrug phases: systemic arterial hematocrits, systemic arterial oxygen saturations, respiratory quotients, oxygen consumptions, ventilations, and total plasma and total blood volumes.

Outputs of urine and intakes of fluid were measured during the control and immediate postdrug phases. The patients received 450 to 500 c.c. of isotonic glucose intravenously at a constant rate during the entire study. The outputs of urine increased by 40 to 400 c.c. (average 196 c.c.) during the immediate postdrug phases as compared to control periods. In Patients 8 and 9, total outputs of urine exceeded intakes of fluid by 75 to 100 c.c., whereas in Patients 10, 11, and 12 the intakes of fluid exceeded the outputs of urine by 135 to 260 c.c. In Patient 9, concentrations of sodium and chloride in the urine increased fivefold, and the concentration of potassium, twofold during the immediate postdrug phases; and in Patient 11 there was a slight increase in the urinary concentration of sodium, a fivefold increase in the concentration of potassium, and a twofold increase in the concentration of chloride.

## Discussion

Conflicting interpretations have been offered to explain the mechanisms by which chlorothiazide exerts its antihypertensive action. Probably the most important single question has been whether this drug reduces blood pressure by producing oligemia or by a direct vasodilatory effect, or by a combination of these factors.

It has been proposed that the chlorothiazide-induced oligemia is responsible for the reduction in blood pressure.[8-11] Freis and co-workers[8,9] call attention to the parallelism between electrolyte and fluid (urine) losses, reductions in extracellular

fluid and plasma volumes, and the decreases in blood pressure. In addition, the withdrawal of chlorothiazide results in a prompt increase in plasma volume and a rise in blood pressure.[9] Infusions of Dextran have been given to some hypertensive subjects in whom the blood pressure was lowered by chlorothiazide, and this resulted in immediate rises in blood pressures and decreases in hematocrits.[9,10] Dustan and associates[10] and Heider and associates[11] suggest that the primary factor in determining chlorothiazide enhancement of the hypotensive effects of ganglioplegic drugs is the contraction of plasma volume which ncreases vasomotor tone and, hence, makes the patient more responsive to the latter drugs.

Observations by others have suggested that the antihypertensive effect of chlorothiazide cannot be explained solely on the basis of oligemia, and that there may also be a distinct action of this drug, directly or indirectly, on blood vessels. Wilkins and co-workers[12,13,14] have demonstrated that the decline in blood pressure during chlorothiazide therapy may not parallel closely the degree of depletion of electrolytes and water from the body. They have also shown that after prolonged periods of therapy the hypotensive effect may persist without accompanying reductions in body sodium and potassium, extracellular fluid, and plasma volume. The simultaneous administration of 9-alpha fluorohydrocortisone and chlorothiazide in a hypertensive subject resulted in a positive sodium balance, no changes in body weight, but a reduction in blood pressure.[12] A reduction in blood pressure may occur within a few hours after the drug has been administered, without significant changes in weight, especially in subjects who had previously had splanchnicectomy.[12-14] In another group of hypertensive subjects, decreases in plasma volumes, blood pressures, and cardiac outputs occurred after 7 to 19 days of therapy.[15] Plasma volumes and cardiac outputs rose to control levels after 1 month, but blood pressures remained reduced. Crosley and co-workers[16] administered chlorothiazide intravenously to a group of subjects with hypertension. Within 15 to 30 minutes, significant decreases in glomerular filtration rate, renal blood flow, and cardiac output occurred. Systemic arterial pressures did not change due to increases in total peripheral resistances. Hematocrits did not change, implying constant plasma volumes.[16]

The results of the present study offer further evidence that chlorothiazide has distinct vasodepressor effects, apart from those attributable to oligemia. In those hypertensive subjects in whom chlorothiazide lowered the blood pressure there were no changes in total plasma and blood volumes as indicated by constant hematocrit values and by direct measurements ($I^{131}$-labeled human serum albumin). Although the drug induced salt and water diureses in all but one (Patient 4) of the subjects in whom this was measured, there were no consistent relationships between changes in fluid balance and changes in blood pressure. In most subjects in whom hypotension was induced, diureses and negative fluid balances occurred; however, in Patient 1 an increase of only 70 c.c. in the output of urine occurred, and the intake of fluid exceeded the total output of urine by 330 c.c. In the hypertensive and normotensive subjects in whom blood pressures did not change during the immediate postdrug phases, diureses were induced by the drug; fluid balances were negative in 2 patients (Nos. 8, 9) and positive in 3 (Nos. 10-12).

The reductions in blood pressures were caused primarily by decreases in cardiac outputs. Reductions in stroke volumes were responsible for the decreases in cardiac outputs. The mechanisms whereby cardiac outputs (or stroke volumes) were reduced are not readily apparent from the data available. Oligemia does not appear to be the major factor, for the reasons stated above. Another possibility is a decrease in interstitial fluid pressure (secondary to loss of extracellular fluid) which may reduce vascular tone and, thereby, cause vasodilation. Since plasma volume may be considered to be in constant equilibrium with interstitial fluid, the absence of changes in plasma volumes in the subjects of the present study would suggest that this factor was not important. Inhibition of myocardial contractility is a possibility, but the present data do not permit conclusions in this regard. Another interesting possibility is a redistribution of blood volume from

the central vascular bed to peripheral vessels, resulting in a reduction in venous return and, thereby, in the amount of blood available to the heart. This would imply peripheral vasodilation, primarily venous.

In 3 patients (Nos. 1, 2, 7), calculated peripheral resistances decreased, suggesting reductions in arteriolar tone. In 3 others (Nos. 4-6), significant increases in peripheral resistances occurred. The latter, however, does not necessarily indicate increased arteriolar tones, but, rather, decreases in luminal area or caliber. In general, caliber varies indirectly with the active (smooth-muscle dependent) vascular tone and directly with the intravascular force (blood flow or volume) tending to distend the vessel; the result depends on the balance between these two factors.[17] Therefore, a rise in peripheral resistance (or a decrease in luminal caliber) may occur in the presence of a decline in vasomotor tone if the distending force (blood flow or volume) decreases to a greater degree.[17] This may well have occurred in our subjects. It was previously noted that the declines in cardiac outputs were considerably greater in the patients in whom calculated peripheral resistances rose than in those in whom resistances fell, implying that the arteriolar distending force was less in the former patients, contributing to decreases in arteriolar caliber independent of tone. In addition, arterial pressure is ordinarily maintained in the presence of diminished cardiac output by a *compensatory* rise in arteriolar tone (and peripheral resistance). That blood pressures declined in our subjects again suggests that active compensatory arteriolar constriction was impeded by reductions in arteriolar tone.

The declines in pulmonary arterial, pulmonary "wedge," and right ventricular pressures (Group A) appear to have been due to decreases in central blood volumes and cardiac outputs. Pulmonary "arteriolar" resistances did not change. Significant changes in these pressures were primarily limited to those subjects in whom they were elevated in the control states. This could be explained as a function of the volume-elasticity properties of the pulmonary vessels and heart chambers whose pressure-volume curves are characterized by upward convexities when pressure is plotted on the vertical axis.[18-20] Thus, when pressures are initially normal, changes in volume produce minimal changes in pressure, frequently to such a slight degree as to be within the limits of technical errors in measurement. In contrast, small changes in volume may accomplish large changes in pressures when the latter are initially elevated.

These studies refer to the changes in cardiovascular dynamics during the immediate period (as defined above) after the administration of chlorothiazide. The results do not necessarily relate to effects during long-term drug therapy. However, other investigators[12-15] suggest that distinct vascular effects play a role probably for as long as the drug is administered.

## Summary

The acute effects of chlorothiazide upon cardiovascular dynamics were studied in 10 patients with systemic hypertension and in 2 normotensive subjects. Measurements were made before and after (the immediate postdrug phase) the intravenous administration of chlorothiazide. Fluid balances were also evaluated before and after administration of the drug.

In 7 patients (Group A), significant declines in systemic arterial pressures occurred during the immediate postdrug phases. These patients had pre-existing hypertension. In most instances, these changes in pressures were due to reductions in cardiac outputs (or stroke volumes). In 3 subjects there were significant declines in total peripheral resistances, suggesting reductions in peripheral arteriolar tone. In 3 others, peripheral resistances increased. It is believed that the increased resistances in the latter patients probably were due to passive reductions in arteriolar caliber (as a consequence of reductions in flow) rather than to increases in tone. Central vascular pressures decreased in those subjects in whom they were initially elevated. This appeared to be related to the decreases in cardiac outputs and central blood volumes. Plasma and blood volumes did not change in those patients in whom they were measured. There were no consistent relationships between fluid balances and changes in cardiodynamics.

In 5 subjects (Group B) there were no changes in systemic arterial pressures during the immediate postdrug phases. Three of these patients had pre-existing hypertension, and 2 were normotensive. Plasma and blood volumes did not change. Fluid balances were similar to those of Group A.

The data suggest that the mechanisms of the antihypertensive action of chlorothiazide include distinct vascular (vasodilating) effects, apart from the role oligemia may have. These vascular effects of the drug appear to depend on the existence of the hypertensive state. The exact nature of these effects are unknown, although various possibilities are discussed.

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# Experimental study on ventricular extrasystoles provoked by vagal stimulation

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Carotid sinus pressure occasionally leads to the appearance of extrasystoles. They can be elicited and registered electrocardiographically in some patients during or shortly after carotid sinus pressure, thus confirming a clinical diagnosis. Both experimentally and clinically these ectopic beats are most often of ventricular origin. This is of interest since vagus fibers are said to be nonexistent in the ventricles, and vagal effects on the ventricles of the mammalian heart are generally absent. Investigations with the myocardiograph of Cushny[3] and measurements of intraventricular pressure[21] showed no effect of vagal stimulation on cardiac contractility.

An experimental study of the effect of vagal stimulation on ventricular extrasystoles was undertaken on dogs in 1929.[22] A solution of aconitine in distilled water was injected intravenously. Before any change in rate, rhythm, or form of the complexes was noticeable, vagal stimulation regularly elicited the appearance of a bigeminal ventricular rhythm. When the bigeminal rhythm was well established, stimulation of the vagus led to an increase in the number of ectopic beats after a normal complex. This effect was immediate and reproducible. However, it was not possible to generalize from these experiments, since aconitine extrasystoles showed "paradoxical" response to other measures. They disappeared promptly on sympathetic stimulation, and their number increased under the influence of choline or potassium. In view of these findings, we undertook the study of the effect of vagal stimulation on ventricular extrasystoles provoked by other substances.

In experiments in which a 20 or 30 per cent solution of sodium chloride was applied focally to the ventricle of the exposed heart of the dog a paroxysmal ventricular tachycardia appeared, which originated in the treated area.[19] The decision was made to study the effect of vagal stimulation on these extrasystoles.

## Method

Dogs which weighed between 10 and 15 kilograms were anesthetized with intraperitoneal sodium pentobarbital (18 mg./Kg.) and morphine (8 mg./Kg.). The chest was opened after artificial respiration had been instituted, and the heart was exposed. The right vagus was attached to a shielded electrode. Injection of 0.01 c.c. of a 20 per cent solution of sodium chloride was made into a small area near the surface of the right or left ventricle. The ECG was registered in Lead II.

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## Results

In most experiments there was an immediate ventricular tachycardia. This generally subsided within 1 or 2 minutes. To avoid the period during which chance recurrence of the tachycardia was likely, vagal stimulation was not applied during the first 2 or 3 minutes after injection of the salt solution. In some experiments no tachycardia developed after the application of sodium chloride, and in such cases the vagal stimulation elicited the arrhythmia. In most experiments the effects were reproducible. Thus, the effect of vagal stimulation seen in Fig. 1 could be elicited five additional times. About 8 to 10 minutes after the end of the tachycardia, vagal stimulation failed to provoke extrasystoles.

Fig. 1 was obtained in an experiment in which an attempt was made to inject the solution of sodium chloride into the area of the atrioventricular node near the coronary sinus vein. This resulted at first in a ventricular tachycardia which was caused by some of the sodium chloride reaching the base of the right ventricle (Fig. 1,*A*). After the tachycardia ended, an atrioventricular rhythm without extrasystoles appeared. Vagal stimulation (Fig. 1,*B*) inhibited this rhythm and elicited groups of bigeminy and trigeminy with the same extrasystoles which caused the preceding ventricular tachycardia (Fig. 1,*B-D*). After eleven such groups, atrioventricular rhythm and sinus rhythm reappeared. Renewed vagal stimulation had the same result.

An important fact in these experiments is that the interval between the extrasystoles caused by vagal stimulation is very short (Fig. 2). In this experiment the interval measures 0.16 second, which corresponds to a heart rate of 375 beats per minute. Here, as in other experiments, the extrasystoles disappeared immediately after the end of the stimulation. These characteristics rule out the possibility that these extrasystoles could have been ectopic beats which escaped from the lower centers because of the slowing of the heart. The coupling in our experiments was so short that they could have appeared even if the heart rate had not decreased during vagal stimulation.

Fig. 3, obtained in the course of another experiment, showed the appearance of multiple extrasystoles during vagal stimulation. The extrasystoles caused by the application of sodium chloride without vagal stimulation never exhibited this rapid rate; they would beat at about 180 per minute, whereas after vagal stimulation the rate could become very much faster. In Fig. 3 the interval between the second and third extrasystoles is 0.12 second, corresponding to a rate of 500 beats per minute.

In Fig. 4 the extrasystoles brought out by vagal stimulation appeared in groups.[24] Pairs of ectopic beats are separated by pauses of variable duration. After the end of vagal stimulation at the beginning of Fig. 4,*B* there are multiple extrasystoles coupled to the sinus beats. Again in this instance the interectopic interval and the coupling are such that the abnormal beats could have appeared even if the heart had not been slowed by vagal stimulation.

The same rapid rate of extrasystoles is again in evidence in Fig. 5 after vagal stimulation. In this experiment, we see left ventricular extrasystoles as the sodium chloride was applied to the left ventricle.

This effect of vagal stimulation was observed in 11 out of 24 experiments.

## Discussion

The results of these experiments show that extrasystoles caused by focal administration of hypertonic sodium chloride reappear during vagal stimulation, usually with a much faster rate. Whereas aconitine extrasystoles which were elicited in a similar manner persisted for a long time after cessation of the vagal stimulation, the extrasystoles in the present experiments disappeared immediately or within a few seconds. There is no doubt that we are dealing with true extrasystoles, that is, with beats elicited by the previous beat. Previous experimental studies on the effect of vagal stimulation and vagal reflexes on the appearance of extrasystoles are discussed elsewhere[25] and will therefore not be analyzed here. We stress only the investigations of Hering,[7] Heymans,[8] and Schott[26] on carotid sinus stimulation and extrasystoles in the rabbit. Ventricular extrasystoles may appear or disappear during vagal stimulation, and, in a previous

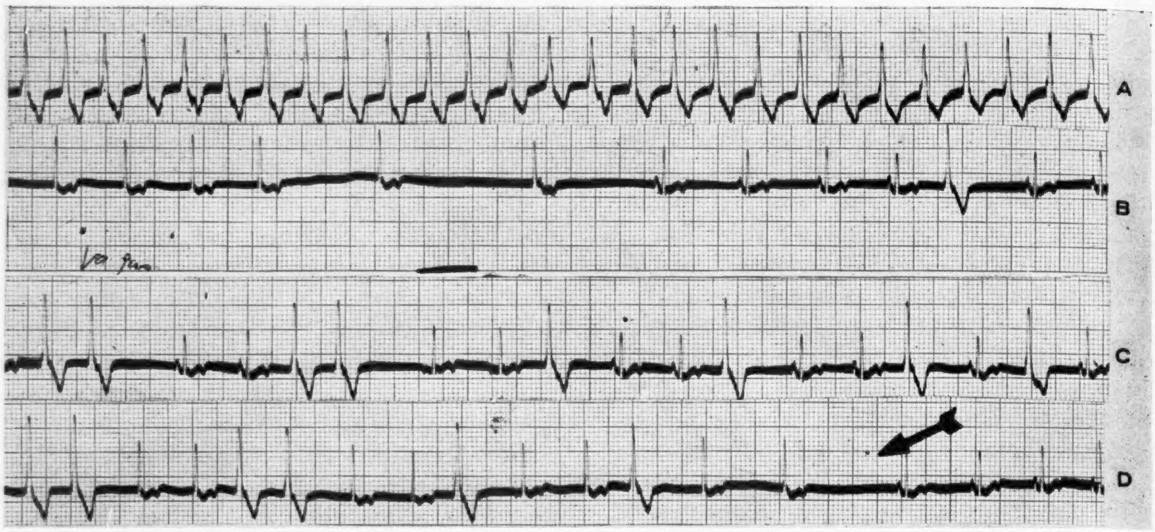


Fig. *1*. *A* shows a ventricular tachycardia which appeared after the injection of 0.05 c.c. of a 20 per cent solution of sodium chloride into the posterior aspect of the right ventricle near the atrioventricular groove. The rate is 175 beats per minute. After the end of this tachycardia an atrioventricular rhythm appeared. Vagal stimulation slowed the rate, and sinus rhythm soon reappeared, with extrasystoles which followed the preceding sinus beat after a coupling of 0.36 to 0.40 second. The extrasystoles disappeared after a few seconds, but reappeared in the same manner during five consecutive stimulations.

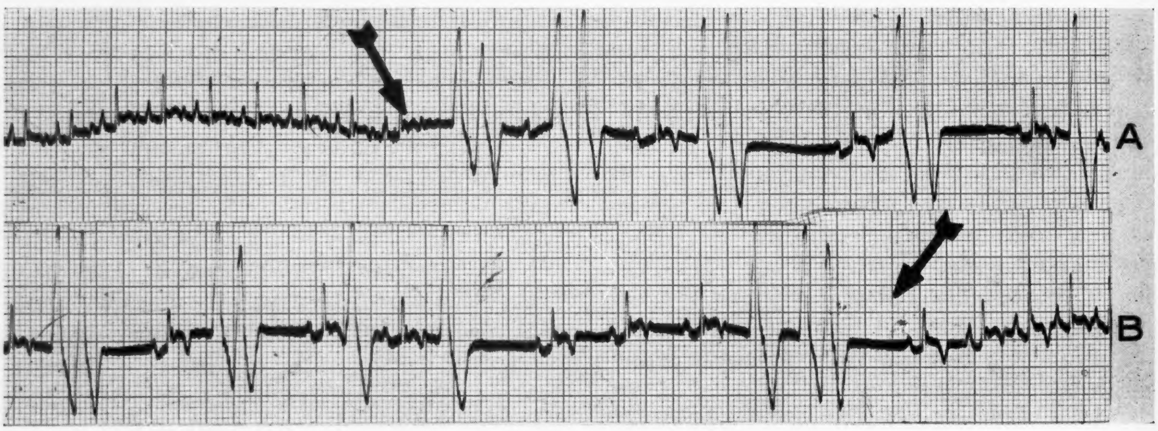


Fig. *2*. *A* and *B* are continuous tracings. *A* shows a sinus tachycardia of 166 beats per minute. Vagal stimulation leads immediately to the appearance of ventricular extrasystoles in the form of trigeminal groups. The extrasystoles disappear immediately after the end of the stimulation (last part of *B*). The first extrasystole appears after a coupling of 0.38 second. It varies in the other beats, and is only 0.16 second in *B*. The distance between two extrasystoles is as short as 0.16 second, which corresponds to a rate of 375 beats per minute.

report, we demonstrated the reappearance of a ventricular tachycardia upon such stimulation after the application of a 30 per cent solution of sodium chloride to the surface of the ventricle.[19]

Vagal stimulation in the dog elicited similar rapid extrasystoles without premedication, at least in one experiment,[13] and similar bursts of rapid extrasystoles have been seen in man during compression of the carotid sinus region.[27]

Textbooks generally state that carotid sinus pressure is of no effect in ventricular tachycardias. Although this is usually true, there is a well-documented observation reported by Wenckebach and Winterberg,[29] in which a ventricular tachycardia could be stopped by carotid pressure. In another study,[20] mechanical irritation of the respiratory tract caused the appearance of ventricular extrasystoles. Carotid pressure or eyeball pressure could pro-

voke groups of rapid ventricular extrasystoles,[9,12,14] or abolish them if they were already present.[1] Even such substances as calcium or potassium will cause or abolish extrasystoles, depending on the condition of the experiment.

A stimulating effect of the vagus on ventricular extrasystoles was observed in the dog after intravenous injection of digitalis and after administration of calcium chloride.[11] When a solution of sodium chloride is applied to the atria, vagal stimulation leads regularly to atrial fibrillation.[23]

Vagal effects on ventricular impulse formation and ventricular conduction have been reported in several older observations. Erlanger observed a slight chronotropic effect of vagal stimulation during heart block, and this was confirmed.[10,17 18] In man, the injection of a choline ester, carbamylcholine chloride, was shown to slow the ectopic rhythm in parasystole,[4] and

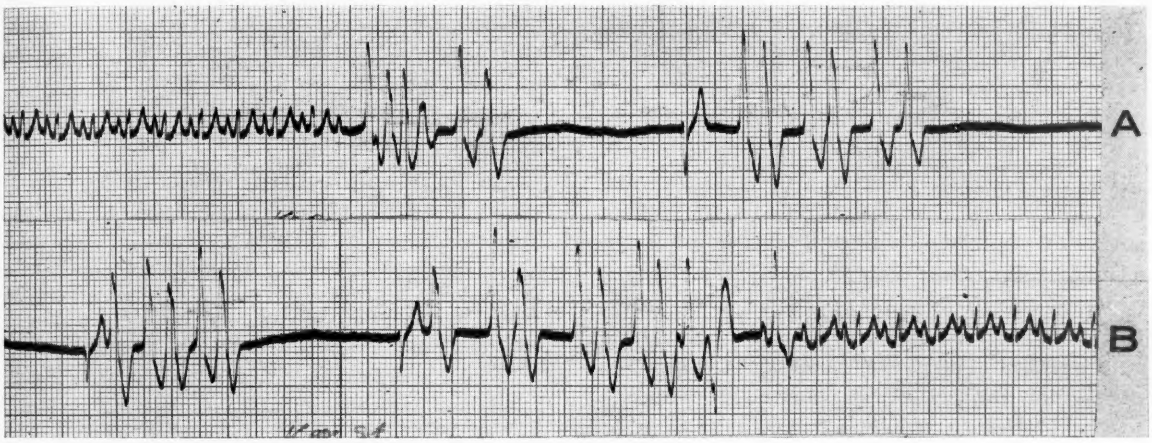


Fig. *3*. There is a sinus tachycardia with a rate of 214. Vagal stimulation leads to a burst of ventricular extrasystoles with a rate up to 500 per minute. After this burst, coupled beats appear, following after 0.20 second the preceding automatic beat. The first extrasystole follows the preceding sinus beat after 0.40 second.

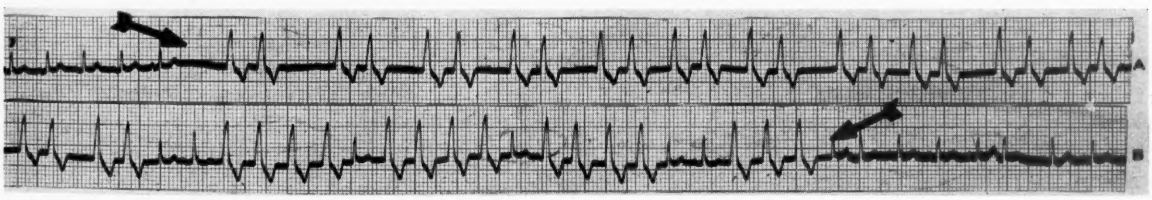


Fig. *4*. Vagal stimulation in this experiment caused the appearance of extrasystoles in groups. After the end of the vagal stimulation (first third of *B*), coupled extrasystoles appear, followed by sinus rhythm with an occasional atrial extrasystole. The two tracings are continuous.

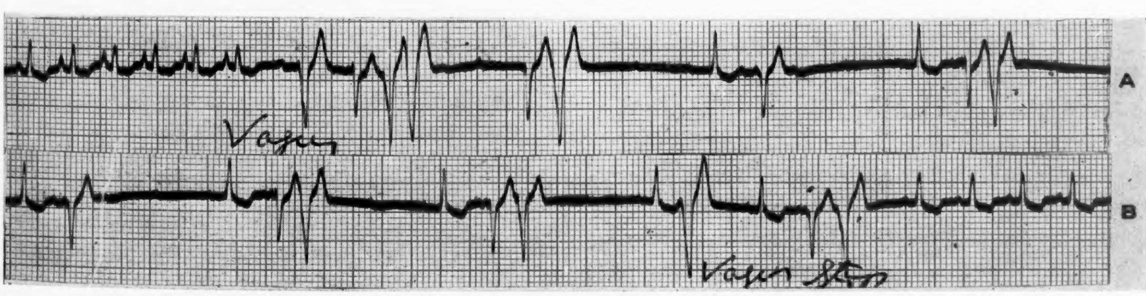


Fig. *5*. In this experiment the solution of sodium chloride had been applied to the left ventricle. Here vagal stimulation elicited left ventricular extrasystoles with rapid rates.

we have repeatedly observed the slowing of parasystolic ventricular centers by carotid pressure. The influence of carotid pressure on bundle branch block has been discussed by Dressler.[2]

The mechanism of the appearance of ventricular extrasystoles during vagal stimulation is not clear. This same phenomenon in the aconitine experiments was explained by the release of acetylcholine in the atria, which led in a sensitized ventricle to an abnormal response to the minute amounts of acetylcholine reaching it.[22] Acetylcholine reduces the resistance of membranes and increases their permeability for potassium.[28] This may facilitate the appearance of afterpotentials and, therefore, of extrasystoles. It may be stated in objection to this that extrasystoles are related to changes in rate which result from vagal stimulation, but in Figs. 2 and 3, as well as in several other experiments, the change in rate, the duration of diastole preceding the first extrasystole, was so small that this mechanism is highly improbable. On the other hand, the extrasystoles appear so early after the onset of the vagal stimulation that the amount of acetylcholine reaching the ventricles from the atria can only be very small.

The complete absence of vagal fibers in the mammalian heart has recently been denied.[15,16] It is possible that such fibers, abundant in the lower classes of animals, do appear occasionally as an inherited anomaly.

The extrasystoles in the present series of experiments are centainly not provoked by the stimulation of sympathetic fibers which are said to be found occasionally in the vagus nerve. Against this interpretation speaks their appearance without any latent period immediately after the onset of the vagal stimulation.

The extrasystoles which appeared during vagal stimulation had, as the illustrations show, the same configuration as that of the extrasystoles which were provoked by the application of sodium chloride. They came from the same focus. Minor differences in form are caused by the differences in rate. The rapid rate of these extrasystoles is noteworthy. It was much higher than that observed in extrasystoles caused by focal application of digitalis, strophanthin, sodium chloride, sodium citrate, or oxalate and veratrine.

The extrasystoles described in the present study follow each other so quickly that it seems possible that one extrasystole appearing during the vulnerable period may lead to ventricular fibrillation and sudden death.

## Summary

Ventricular extrasystolic tachycardias were provoked by focal application of a hypertonic solution of sodium chloride on the exposed heart of the dog. After these extrasystoles subsided, faradic stimulation of the right vagus nerve made them reappear. This effect was reproducible. The extrasystoles which were observed during vagal stimulation were identical with those which appeared after the application of sodium chloride. A characteristic feature of these extrasystoles was their unusually high rate.

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# Serum lactescence in normal subjects and in patients with coronary artery disease before and after the administration of sublingual heparin

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It has been recognized since 1943 that intravenous heparin clears hyperlipemic serum.[1] Subsequent work has shown that this effect is due to the activation of a clearing factor or lipoprotein lipase.[2,3] More recently, it has been claimed that heparin given in sublingual form is likewise capable of clearing turbid serum without, however, interfering with the blood-clotting mechanism.[4,5] If this is so, it is possible that sublingual heparin might prove to be of value as an antilipemic agent in the management of patients with ischemic heart disease, especially since anginal attacks induced by the ingestion of fat can be promptly arrested by injections of this drug.[6] In the light of these observations, the decision was made to measure the lactescence of postprandial serum in a group of healthy subjects as well as in a series of patients with coronary artery disease before and after the administration of heparin by the sublingual route.

## Material and Methods

The group of subjects in apparent good health consisted of 32 men and 8 women who were between the ages of 20 and 68 years (average age, 47 years). The series of patients with coronary artery disease comprised 21 men and 4 women, whose age distribution was 35 to 72 years (average age, 53 years). All patients with ischemic heart disease had developed electrocardiographic evidence of an acute myocardial infarction within the previous 6 weeks.

Optical densities of centrifuged citrated serum were measured by means of a "Spekker" spectrophotometer (using a red filter at a wave length of 740 millimicrons). Control values were first established for each individual by measuring the serum turbidity when he was in the fasting state and at 2, 3, 4, 5, and 6 hours after he had ingested a standard meal of fat; this routine was then repeated within a period of 1 week, with the addition that the subject was given one tablet of heparin (1,500 I.U.*) at the following times: (1) immediately after the meal; (2) one-half hour after the meal; and (3) 1 hour after the meal. Thus, each subject received a total dosage of 4,500 I.U. of sublingual heparin during the second experiment. The individuals taking part in this trial clearly understood the importance of retaining the tablets under the tongue and/or in the buccal pouch; furthermore, each subject was requested to avoid swallowing saliva, in so far as possible, until disintegration of the tablets was complete. Twenty-five of the healthy subjects were

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given 3 ounces of lipid emulsion (containing egg yolk, soya, lecithin, glycerin, and peanut oil) as a source of fat. Eighteen of the individuals in this group were ambulant and were allowed to continue with normal physical activities between each venipuncture. The other 7 subjects rested in bed during the study. The other volunteers (15 healthy subjects and 25 patients with coronary artery disease) took 4 ounces of milk and 4 ounces of "double" cream (i.e., 60, Gm. of fat). All the members of this group, with the exception of 5 healthy subjects, were confined to bed throughout the study, as well as for 24 hours beforehand. Care was taken to ensure that the entire quantity of fat was consumed on each occasion. Every individual fasted for at least 9 hours before the first specimen of blood was withdrawn, as well as throughout the experiment, with the exception of the standard meal of fat.

The clotting time of the blood was determined by the Lee and White method.

## Results

It is evident from Tables I and II that the mean values for serum turbidity recorded in the healthy subjects after the administration of sublingual heparin were essentially similar to those obtained during the control experiments, irrespective of whether the lipid emulsion or milk and cream was employed as the source of fat.

Table III demonstrates that there was no significant difference between the mean values for serum turbidity before and after the administration of sublingual heparin in the patients with coronary artery disease.

Comparison of the values presented in Tables II and III indicates that the postprandial turbidity of the serum was more intense and prolonged in the series of patients with ischemic heart disease than in the group of healthy subjects, irrespective of the administration of heparin.

The clotting time of the blood was determined when the subjects were in the fasting state, and at 3 and 5 hours post-

*Table* I.* *Average serum turbidity after 3 oz. of lipid emulsion in 25 healthy subjects*

| | *Fasting* | *2 hr.* | *3 hr.* | *4 hr.* | *5 hr.* | *6 hr.* |
|---|---|---|---|---|---|---|
| Control values | 0.041 | 0.184 | 0.324 | 0.278 | 0.214 | 0.080 |
| Values after 4,500 I.U. of sublingual heparin | 0.043 | 0.190 | 0.326 | 0.264 | 0.208 | 0.084 |

*For the sake of brevity, the values for serum turbidity in individual subjects and patients have not been included in the tables of this publication, although they are available on request.

*Table* II. *Average serum turbidity after 4 oz. of milk and 4 oz. of cream in 15 healthy subjects*

| | *Fasting* | *2 hr.* | *3 hr.* | *4 hr.* | *5 hr.* | *6 hr.* |
|---|---|---|---|---|---|---|
| Control values | 0.048 | 0.253 | 0.424 | 0.334 | 0.246 | 0.130 |
| Values after 4,500 I.U. of sublingual heparin | 0.044 | 0.240 | 0.418 | 0.326 | 0.258 | 0.125 |

*Table* III. *Average serum turbidity after 4 oz. of milk and 4 oz. of cream in 25 patients with coronary artery disease*

| | *Fasting* | *2 hr.* | *3 hr.* | *4 hr.* | *5 hr.* | *6 hr.* |
|---|---|---|---|---|---|---|
| Control values | 0.070 | 0.358 | 0.550 | 0.594 | 0.512 | 0.374 |
| Values after 4,500 I.U. of sublingual heparin | 0.069 | 0.340 | 0.554 | 0.586 | 0.520 | 0.385 |

prandially in 10 of the healthy subjects, both during the control experiments and after the administration of sublingual heparin. No significant alterations in the clotting time were recorded in any of the individuals concerned.

## Discussion

Previous claims[4,5] as to the efficacy of sublingual heparin in enhancing the clarification of postprandial lipemic serum could not be confirmed in the present study, either in the group of healthy subjects or in the series of patients with coronary artery disease. It seems unlikely that this discrepancy arose as a result of inadequate dosage, for in this investigation each individual received a total quantity of 4,500 I.U. of heparin, whereas Fuller[4] and Shaftel and Selman[5] reported a pronounced effect after the administration of only 1,500 I.U. of this material. Furthermore, the lipid emulsion used as a standard load of fat in 25 of the healthy subjects in the series under review was identical with that employed by these workers. Nevertheless, in the present study the opportunity was also taken to assess the effect of sublingual heparin after a meal which consisted of milk and cream, since a preparation of this type is unlikely to gain acceptance as a fat-clearing agent of practicable value unless it can be shown to promote the clarification of lipemic serum which results from the ingestion of lipids commonly found in the average diet. (The lipid emulsion utilized by Fuller[4] and Shaftel and Selman[5] as well as by the present investigator in 25 of the healthy subjects must be regarded as a highly artificial preparation.)

The failure of sublingual heparin to promote significant clarification of hyperlipemic serum in the present series finds some support from the results published by Engelberg.[7] This investigator measured the plasma-lipemic "clearing" and lipolytic activity of triglyceride in 21 subjects, as well as the levels of heparin in the plasma of 13 individuals before and after the administration of 1,500 I.U. of sublingual heparin. A significant degree of absorption was demonstrated in only 3 patients. On the other hand, the administration of even small amounts of intravenous heparin led to a definite increase in the "clearing" and lipolytic activity of the blood. Engelberg suggested that the divergence between his results and those of Fuller[4] was probably due either to the fat-clearing action of other mucinous polysaccharides contained in the heparin preparation or to the failure of Fuller to use placebo tablets in his control observations.

The absence of a significant alteration in the clotting time of the blood after the administration of sublingual heparin in the present study is in agreement with the results of other workers.[4,5,7] According to Engelberg,[7] the failure of even large doses of sublingual heparin to induce an anticoagulant effect[4,5] provides additional evidence against any substantial absorption by this route, inasmuch as a recent report[8] suggested that the amount of intravenous heparin required to influence the clotting mechanism is no greater than that necessary for lipemia "clearing" (except for very small doses below 3 mg.).

Irrespective of the administration of sublingual heparin, however, the present study did reveal that ingestion of a standard quantity of fat has a much more marked effect on the serum turbidity of patients with ischemic heart disease than on that of healthy persons. Although the individuals in this series were not age-matched, it may be noted that there was in fact comparatively little disparity in the average age between the two groups of subjects. Reduction of the tolerance for fat in patients with coronary artery disease has likewise been reported by other workers, including Woldow and associates,[9] Barritt,[10] and Mitchell and Bronte-Stewart.[11] However, the relevance of these observations in regard to the pathogenesis of coronary occlusive disease must as yet remain conjectural. The mechanism of increased alimentary lipemia in these patients is also far from certain. Thus, according to Block and associates,[12] the heparin-activated enzyme system may well be defective in patients with atheroma. On the other hand, Hood and co-workers,[13] Kaufmann,[14] and Baker[15] were unable to demonstrate any difference in the clearing-factor activity between normal control subjects and patients with coronary artery disease. It is of interest, too, that Becker and associates[16] have shown that intra-

venous fat disappears from the plasma at the same rate in patients with widely different degrees of alimentary lipemia. Recently, Mitchell and Bronte-Stewart[11] have suggested that the very intense lipemia which develops in patients with ischemic heart disease depends upon a difference in the rate of absorption of fat in these patients rather than upon a difference in the rate of removal.

**Summary**

The lactescence of postprandial serum was measured in 40 healthy subjects as well as in 25 patients with coronary artery disease, before and after the administration of sublingual heparin (4,500 I.U.). Twenty-five of the healthy subjects were given 3 ounces of lipid emulsion as a standard load of fat; the other individuals received 4 ounces of milk and 4 ounces of "double" cream (i.e., 60 Gm. of fat).

The average degree of postprandial serum turbidity after the administration of sublingual heparin was not found to differ significantly from that observed during the control experiments, either in the series of healthy subjects or in the group of patients with ischemic heart disease.

No significant alterations in the whole blood clotting time were demonstrated in 10 healthy subjects who received sublingual heparin.

Irrespective of the administration of heparin, ingestion of a standard meal of fat produced a much more pronounced effect on the serum turbidity of patients with coronary artery disease than on that of the healthy subjects.

I wish to thank Dr. Shirley Smith for allowing me to study his patients with coronary artery disease. I am also grateful to the Clinical Research Committee of Charing Cross Hospital for providing facilities which enabled this research to be performed.

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# Digitalis and the pulmonary circulation

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Although much is known about the effects of digitalis on the heart, the effects on the pulmonary circulation are quite uncertain. In anesthetized dogs the intravenous injection of various digitalis preparations has been shown to cause an increase in pulmonary arterial pressure.[1-3] On the other hand, subsequent reports on patients who have heart disease, and who usually are in heart failure, show largely a decrease in pulmonary arterial pressure (see references[4]). These differences may be related to the differences in species or to pre-existing disease states. The effects of digitalis can be defined by a systematic comparison of the following determinants of the pulmonary circulation in human beings and in dogs: (a) pulmonary arterial pressure, (b) pulmonary venous pressure, (c) pulmonary blood flow, and (d) the derived pulmonary vascular resistance. In man the measurements of (b) and (c) and the derivation of (d) are indirect in nature, which necessitates the qualification of conclusions in the investigation of mechanisms. On the other hand, the corresponding techniques in dogs are direct and allow the identification of the various causes for the observed hemodynamic effects of digitalis. The specific effects of digitalis on pulmonary blood flow and pulmonary blood vascular resistance in the dog are described and the role of nervous and non-nervous factors are identified.

## Methods

Dogs were anesthetized with morphine (2 mg. per kilogram, subcutaneously) and chloralose (70 mg. per kilogram, intravenously). The following procedures were routinely performed on all animals: (a) cannulation of the trachea to allow the use of a Starling Ideal Pump; (b) cannulation of a femoral vein for drug injection; (c) catheterization of a carotid artery for recording of aortic blood pressure by a Statham transducer; and (d) opening of the chest in the left fifth intercostal space to allow measurements of pressures in the pulmonary artery and left atrium from catheters tied into the vessels of the left upper lobe. The additional procedures performed in each of two groups of dogs consisted of the following:

*1. Measurement of pulmonary venous outflow* (*8 dogs*). This was recorded by a method described previously.[5] All the effluent blood (from the vein of the left lower lobe) was collected in a collapsible rubber reservoir and returned to the ani-

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mal's own left atrium or femoral vein by means of a Sigmamotor pump. The pump was manually adjusted to empty the reservoir continuously and this was checked by visual inspection. A Shipley-Wilson rotameter was inserted into the outflow side of the pump. The above-mentioned system records mean blood flow and does not indicate the pulsatile character of the flow. Manuronate (10 mg. per kilogram, intravenously) was routinely used as the anticoagulant.

*2. Inflow perfusion of the left lower lobe (14 dogs).* The artery to the left lower lobe was cannulated and supplied with blood from the dog's own right atrium, through a Sigmamotor pump. The perfusion pressure was recorded by means of a side arm attached to a Statham transducer.

The following digitalis preparations were injected either intravenously (femoral vein) or directly into the perfused pulmonary artery: acetyl strophanthidin* (0.025 to 0.075 mg. per kilogram), digoxin† (0.1 mg. per kilogram), and ouabain (0.035 mg. per kilogram). Denervation of the lungs was accomplished by combined bilateral cervical vagotomy and excision of the 4 upper thoracic sympathetic ganglia. In some dogs, atropine sulfate (1 mg. per kilogram) and bretylium tosylate† (5 mg. per kilogram) were used for selective blockade of the parasympathetic and sympathetic nerves, respectively.

## Results

*Pulmonary arterial blood pressure.* The typical effect of acetyl strophanthidin is depicted in Fig. 1. Within 2 minutes after the intravenous injection of 0.05 mg. per kilogram there was a slight fall in systemic blood pressure and pulmonary arterial pressure. The subsequent behavior of both pressures for the same dog is shown in Fig. 2, which also shows that both pressures do not run parallel. The systemic pressure rises in a few minutes, but the pulmonary arterial pressure remains low. This fact serves to emphasize the dissimilarities in control between the systemic and pulmonary circulation and more of this will be discussed below.

*Supplied by Dr. K. K. Chen, Lilly Research Laboratories.
†Supplied by General J. Wood, Burroughs-Wellcome Laboratories.

A total of 5 intact dogs was tested and the results are summarized in Table I. Four dogs showed a fall in pulmonary arterial pressure, and one showed no change. The lack of consistency of fall in all dogs could not be explained on the basis of this group of dogs, but became understandable when the perfusion experiments were completed. It is important to point out here that the fall in pulmonary arterial pressure (encountered in 4 out of 5 dogs) is strikingly similar to the observations in man. The similarity also includes the appearance of bradycardia, but not the other measurements, which are discussed in subsequent paragraphs.

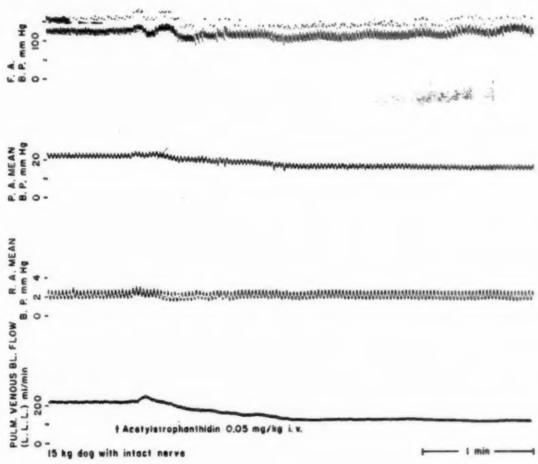


Fig. *1.* Intravenous injection of acetyl strophanthidin causes a reduction in pulmonary arterial pressure and pulmonary venous outflow. Subsequent changes are shown in Fig. 2.

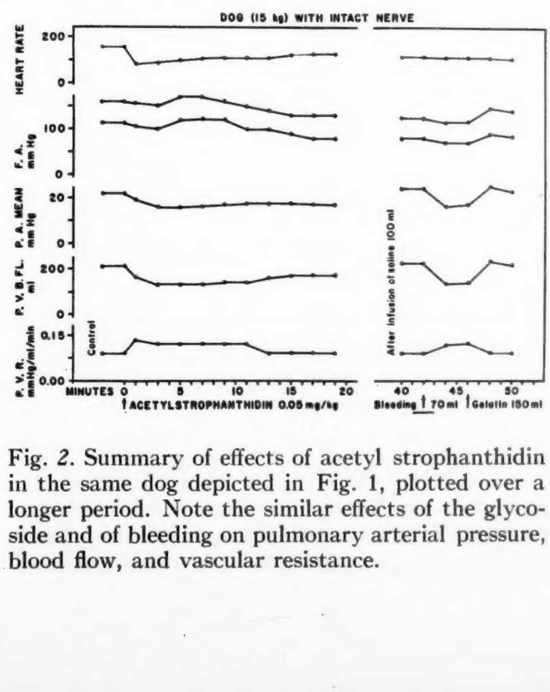


Fig. *2.* Summary of effects of acetyl strophanthidin in the same dog depicted in Fig. 1, plotted over a longer period. Note the similar effects of the glycoside and of bleeding on pulmonary arterial pressure, blood flow, and vascular resistance.

*Table* I. *Results obtained from 5 dogs with intact innervation and 3 other dogs*

| Dog weight (Kg.) | Situation, Drug (mg./Kg.) (min. after) | Mean systemic blood pressure | | Heart rate | | Mean pulmonary arterial blood pressure | | Mean atrial blood pressure (mm. Hg) | | Pulmonary venous flow | | Pulmonary vascular resistance | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | mm. Hg | %Δ | Per min. | %Δ | mm. Hg | %Δ | Left | Right | ml./min. | %Δ | P/F | %Δ |
| 13 | Control | 100 | | 130 | | 23 | | 5.5 | | 330 | | 0.0697 | |
| | Acetyl strophanthidin 0.075 (3 min.) | 125 | +25 | 90 | −30 | 15 | −35 | 4.5 | | 120 | −64 | 0.125 | +81 |
| 18 | Control | 97 | | 200 | | 21 | | 7 | | 220 | | 0.095 | |
| | Acetyl strophanthidin 0.05 (2 min.) | 100 | +3 | 140 | −30 | 21 | 0 | 5 | | 155 | −30 | 0.135 | +42 |
| 15 | Control | 137 | | 162 | | 22 | | | 2.2 | 210 | | 0.104 | |
| | Acetyl strophanthidin 0.05 (4 min.) | 147 | +7 | 86 | −47 | 16 | −27 | | 2.1 | 120 | −42 | 0.133 | +26 |
| 15 | Control | 103 | | 156 | | 18 | | | 7.5 | 230 | | 0.078 | |
| | Acetyl strophanthidin 0.05 (2 min.) | 98 | −5 | 138 | −11 | 17 | −5 | | 6.5 | 160 | −30 | 0.106 | +36 |
| 16 | Control | 115 | | 192 | | 21 | | | 7.5 | 190 | | 0.11 | |
| | Acetyl strophanthidin 0.05 (4 min.) | 93 | −10 | 113 | −41 | 20 | −5 | | 7 | 125 | −34 | 0.16 | +45 |
| | Average %Δ | | +4 | | −31 | | −14 | | | | −40 | | +46 |
| 18 | Vagotomy (control) | 105 | | 222 | | 20 | | | 11 | 320 | | 0.0625 | |
| | Acetyl strophanthidin 0.075* (2 min.) | 185 | +75 | 208 | −6 | 19 | −5 | | 10 | 255 | −20 | 0.0756 | +19 |
| 14 | Bretylium (control) | 135 | | 84 | | 35 | | | 10 | 305 | | 0.114 | |
| | Acetyl strophanthidin 0.07 (2 min.) | 150 | +11 | 50 | −40 | 29 | −17 | | 12.5 | 155 | −46 | 0.187 | +64 |
| 15 | Intact nerve | 130 | | 180 | | 16 | | 7.5 | | 270 | | 0.059 | |
| | Digoxin 0.1 (30 min.) | 125 | −4 | 136 | −32 | 15 | −6 | 7 | | 225 | −16 | 0.067 | +14 |

*Intra-aortic injection; all others are intravenous.

*Left atrial pressure.* It is necessary to consider first the outflow side of the lungs when the cause of a fall in pulmonary arterial pressure is under consideration. The left atrial pressure was measured in 3 dogs, and a fall of 0.5 to 2 mm. was noted However, the intensity of fall in pulmonary arterial pressure is larger by 1 mm. Hg or more, so that one can conclude that the fall in left atrial pressure may contribute slightly to the fall in pulmonary arterial pressure but is not the exclusive cause.

*Pulmonary venous blood flow.* A more important cause for the fall in arterial pressure in the lungs is the reduction in blood flow, which averaged 40 per cent. Experiments were then conducted to detect whether the reduction in pulmonary blood flow was entirely due to cardiac slowing. One dog was vagotomized prior to the administration of acetyl strophanthidin, and another dog after its administration. Cardiac slowing induced by digitalis disappeared, but the reduction in flow still occurred, even when acetyl strophanthidin was injected into the ascending aorta. All these observations exclude two causes for the reduction in pulmonary blood flow: cardiac slowing, and interference in venous return induced by stimulation of cardiac receptors which induce peripheral vasodilatation, a mechanism that has been proposed by Melville.[6] Another explanation, a direct action on systemic vessels to reduce venous return, was not directly proved.

*Pulmonary vascular resistance.* This factor was calculated by simply dividing pulmonary arterial pressure by pulmonary venous flow. No correction for changes in venous pressure was required because the pulmonary venous outflow was collected at the same level as the left atrium and was kept constant. In 5 intact dogs, acetyl strophanthidin caused an increase in calculated vascular resistance (mean +46 per cent). One previously vagotomized dog also showed a similar increase. One additional dog was subjected to chemical sympathectomy by bretylium, and the subsequent injection of acetyl strophanthidin still caused an increase in pulmonary vascular resistance. The results obtained from these 2 dogs indicate the increase in pulmonary vascular resistance. Two possibilities remain: (a) local action of digitalis on the lung vessels, and (b) passive response to a reduction in blood flow. The former could not be tested by simple measurements of blood flow but was studied by lung perfusion (see below). Factor (b) was investigated in the same dogs in which pulmonary blood flow was measured.

*Passive increase in vascular resistance induced by bleeding.* To evaluate the effect which reduced pulmonary blood flow itself (induced by acetyl strophanthidin) had on pulmonary vascular resistance, we compared the effects of the drug with those of reduction in flow by bleeding. In 2 dogs, such a reduction in circulating blood volume by 7 ml. per kilogram caused a reduction in pulmonary blood flow and an increase in vascular resistance (Fig. 2). This increase could be elicited even after digitalization, and even after bretylium. The similarity between the increase in pulmonary vascular resistance induced by acetyl strophanthidin and that induced by bleeding suggests that the reduction in pulmonary blood flow is a cause for the drug-induced increase in vascular resistance, but this does not necessarily exclude a local action of the drug on the pulmonary vessels.

*Pulmonary vasoconstriction of the perfused lung.* The perfusion experiments were performed primarily to administer the drug directly into the pulmonary artery. The next group of experiments consisted of perfusion of the left lower lobe with the animal's own mixed venous blood. A typical response is depicted in Fig. 3, in which acetyl strophanthidin is injected directly into the left lobar artery, perfused at a constant flow. There was a slowly developing rise in pulmonary arterial pressure, which reached its peak 3 minutes after injection. Several other observations should be considered before one can conclude that the increase in perfusion pressure is due to local vasoconstriction.

A. Since alcohol (47.5 per cent, 1 ml.) was used as the solvent for acetyl strophanthidin, alcohol alone was injected as a control procedure, and this did not induce a significant rise in perfusion pressure.

B. The corresponding vein of the perfused left lower lobe remained intact so that, although the drug initially reached the perfused lung, it subsequently reached the left atrium and the systemic circulation. The behavior of the left atrial pressure should be considered as a possible cause for the rise in pulmonary arterial pressure. The left atrial pressure either decreased, was unchanged, or rose much less than did the pulmonary arterial pressure.

C. Because of its systemic effects, acetyl strophanthidin can influence the lungs through its vagal or sympathetic innerva-

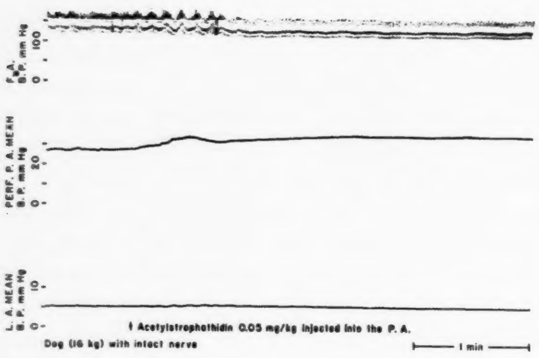

Fig. *3*. Injection directly into the left lower lobe perfused at a constant flow. The initial hump in the perfusion pressure is an injection artifact, but the delayed rise is due to acetyl strophanthidin and is accompanied by no change in left atrial pressure. This record does not include the pulmonary arterial pressure of all the other lobes which are supplied by the dog's own right ventricle.

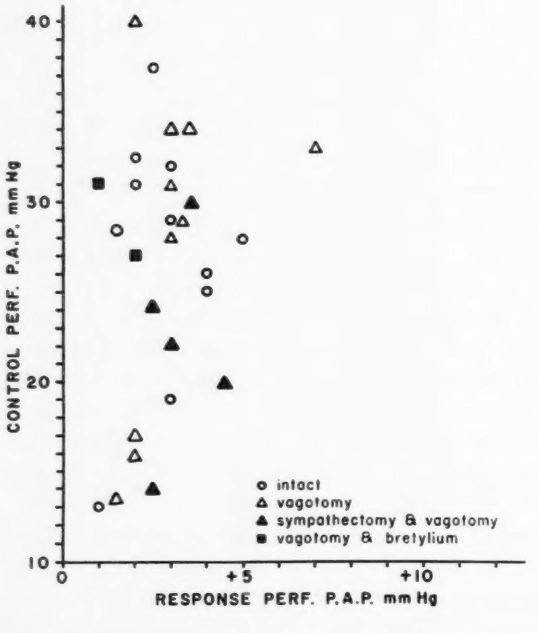


Fig. *4*. Summary of denervation procedures on the pulmonary vasoconstriction induced in the perfused lung by acetyl strophanthidin, 0.05 mg. per kilogram. Note that the vasoconstrictor response occurred even when perfusion pressures were abnormally higher than normal values.

tion. The perfused lung experiment was therefore performed on 14 dogs with a combination of one or two of the following: cervical vagotomy, thoracic sympathectomy, and intravenous injection of bretylium (Fig. 4). These procedures did not interfere with the ability of acetyl strophanthidin to induce a rise in pulmonary arterial perfusion pressure.

D. The increase in vascular resistance induced by acetyl strophanthidin was demonstrated also when the flow to the perfused lobe was intentionally increased or decreased. In each of 5 dogs, a pressure-flow curve was derived before and after digitalis. It can be noted from Fig. 5 that, prior to the drug, the perfused lobe demonstrated the passive decrease in resistance to an intentional increase in flow. Two or three control runs resulted in reproducible pressure-flow curves. After acetyl strophanthidin, a similar curve was derived but at a higher level than the control. There is, therefore, an increase in vascular resistance at all levels of flow tested, and denervation did not influence this effect of acetyl strophanthidin.

E. It has been demonstrated recently that the pulmonary venous junction to the left atrium can be constricted by certain foreign agents.[7] This possibility was tested by measuring pressures separately in the pulmonary vein and left atrium in 6 dogs. Acetyl strophanthidin did not cause a gradient between these two, although the pulmonary arterial pressure increased (Fig. 6).

*Digoxin and ouabain.* These two glycosides were tested in 2 dogs. Digoxin (0.1 mg. per kilogram) caused a reduction in pulmonary blood flow and pulmonary arterial pressure, but an increase in pulmonary vascular resistance (last dog in Table I). Ouabain (0.035 mg. per kilogram) injected directly into the perfused lobe caused local pulmonary vasoconstriction.

## Discussion

The recent availability of a rapidly acting glycoside, acetyl strophanthidin, has allowed the investigation of the effects of digitalis in the pulmonary circulation of the dog. Because the methods used were of a direct nature, which involved vessel cannulation, perfusion, rotameters, and accessory tubings, the effects of the drug must be distinguished from spontaneous deterioration of the preparation. The experiments reported above establish the following actions of acetyl strophanthidin on the pulmonary circulation.

1. Acetyl strophanthidin causes a local vasoconstriction of the perfused lung. This is based on the rise in perfusion arterial

pressure at a constant flow, or on a uniformly higher perfusion pressure at varying flows after the injection of the drug. The exact location of the constriction has not been detected except that the pulmonary venous–left atrial junction can be excluded. In 1914, Macht[8] showed that the medium-sized branch of the pulmonary artery of pigs and oxen was constricted by various digitalis preparations.

2. The increase in pulmonary vascular resistance induced by a local vascular action of acetyl strophanthidin cannot be easily demonstrated by a rise in pulmonary arterial pressure if blood flow is not kept constant. In the intact dog the pulmonary arterial pressure is reduced because of an immediate reduction in pulmonary blood flow. In such situations, the calculation of pulmonary vascular resistance shows an increase after the drug, but it is not possible to attribute this increase to local action because of the passive effect of reduction in flow. It is necessary to explain why earlier investigators[1-3] noted a rise in pulmonary arterial pressure after the intravenous injection of strophanthin, digitoxin, or digitalin. It is probable that the longer latent period resulted in an initial predominance of local vasoconstriction over a delayed reduction in pulmonary blood flow. The use of a rapidly acting glycoside in the experiments reported above caused an early predominance of the latter. As long as digitalis can elicit opposite actions on vessels (constriction) and flow (to reduction), a change in either direction can be expected.

3. Several possible nervous mechanisms can be excluded as a cause for the observed effects of acetyl strophanthidin on the pulmonary circulation. Bradycardia which follows digitalization is not an essential accompaniment for the reduction in pulmonary blood flow because vagotomy does not alter this hemodynamic effect of digitalis. The cause of the reduction in flow appears to be a local action on the systemic vessels, and this has been adequately studied by other investigators.[9,10] The increase in pulmonary vascular resistance, in either the intact animal or in the perfused lung, could also be elicited even after sympathectomy or by blockade with bretylium. This drug has been shown to block the pulmonary vasoconstrictor nerves to the lung vessels,[11] so that one can safely conclude that activation of the sympathetic nervous system is not an important mechanism of the rise in pulmonary vascular resistance.

The foregoing conclusions refer to the lung of the dog, but the situation in the lung of the normal human being is quite uncertain. Digitalization in patients with

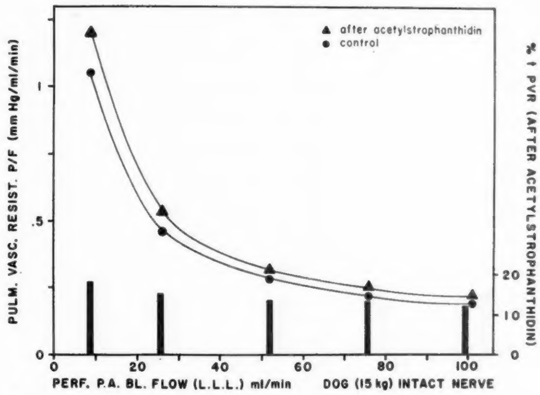


Fig. *5*. Pressure-flow curve of perfused lung at varying flows. Note higher resistance values after acetyl strophanthidin for the same flow values prior to the drug. Only one control run is depicted, but two successive control runs resulted in essentially similar pressure curves.

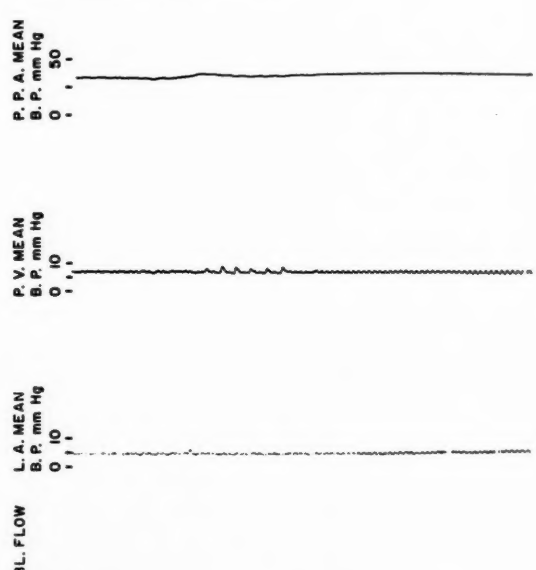


Fig. *6*. Failure of acetyl strophanthidin to elicit a gradient between the pulmonary vein and the left atrium.

congestive heart failure, cor pulmonale, or mitral stenosis has varied effects on the pulmonary circulation, but the majority of patients show a reduction in calculated vascular resistance (see bibliography in Reference 4). If there is local vasoconstriction in the lung of the human being, it is obscured by other factors. An increase in cardiac output usually accompanies the reduction in resistance in the lung of the human being; therefore, such a reduction is probably a passive response to the increase in flow. Also, with improved function of the left heart, and resulting fall in pulmonary venous pressure, there is an apparent fall in pulmonary vascular resistance. Clarification of these possibilities will have to await additional studies in which more direct methods are used to calculate vascular resistance in dogs which are in heart failure and in patients.

## Summary

In anesthetized dogs, the intravenous injection of acetyl strophanthidin caused a slight decrease in pulmonary arterial pressure which could not be explained by the effect on left atrial pressure. There was a marked decrease in the pulmonary venous flow, which was often accompanied by cardiac slowing and an increase in the calculated pulmonary vascular resistance. The cause of the increased pulmonary resistance is a combination of (a) the passive nature due to the decreased blood flow, and (b) local vasoconstriction of the perfused lung. The performance of vagotomy and thoracic sympathectomy, and the intravenous injection of bretylium excluded nervous factors as a cause of the vasoconstriction.

We wish to thank Dr. Calvin F. Kay for his helpful suggestions and advice. The technical assistance of Howard Zaren is deeply appreciated.

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# The effect of ouabain on cardiac automaticity in reserpine-pretreated dogs

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One of the effects of a toxic dose of ouabain is an increase in cardiac automaticity which results in ventricular ectopic beats. Recently, it has been suggested that the increase in cardiac automaticity caused by ouabain may be due to the release of catecholamines from the heart.[1] This suggestion was based on the observation that ouabain usually produced spontaneous beating in the isolated papillary muscle from an untreated cat, but did not cause spontaneous beating in the isolated papillary muscle from cats pretreated with doses of reserpine sufficient to deplete the heart of catecholamines. The amine involved would most likely be norepinephrine.[2]

This study was undertaken to determine whether catecholamines are involved in the mechanism by which ouabain causes ventricular ectopic beats in the dog.

## Methods

Mongrel dogs of both sexes, anesthetized with pentobarbital sodium (30 mg. per kilogram, intravenously), were used in the experiments. The heart rate and rhythm were determined from electrocardiograms (Standard Limb Lead II). The myocardial contractile force was obtained by means of a Walton strain-gauge arch sutured to the surface of the right ventricle.[3] A Sanborn pressure transducer was connected to a carotid artery to measure the blood pressure. The lungs were artificially ventilated by means of a Palmer pump. A femoral vein was cannulated for the injection of compounds. Recordings of the blood pressure, electrocardiogram, and contractile force were made with a Sanborn multichannel recorder.

An aqueous solution of ouabain was used, and each dog received the drug according to the following schedule: an initial dose of ouabain, 40 μg per kilogram, was injected, after which additional doses of 20 μg per kilogram were given every 15 minutes until the appearance of ventricular tachycardia, which was observed for 10 to 15 minutes before the experiment was terminated.

The dogs were divided into three groups. One group of 6 dogs received only ouabain. A second group of 6 dogs was pretreated with reserpine (0.5 mg. per kilogram, intraperitoneally) once a day for 2 days, and was tested on the third day. The reserpine was made up as a 1 per cent solution in 20 per cent ascorbic acid as the solubilizing vehicle. A third group of 3 dogs was pretreated with dichloroisoproterenol (DCI).* A dose of 5 mg. per kilogram was injected intravenously 10 to 15 minutes before the first dose of ouabain was given. The data were analyzed according to the methods of Mainland.[4]

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*Supplied by Dr. Irwin H. Slater, Lilly Research Laboratories, Indianapolis, Ind.

*Table* I. *Response of the heart to ouabain in normal and reserpine-pretreated dogs*

| Dog number | Control: Ventricular rate (beats/min.) | Control: Contractile force (mm.) | Control: Cardiac rhythm | Total dose of ouabain (μg/Kg.) | After ouabain: Ventricular rate (beats/min.) | After ouabain: Maximum increase in heart rate (%) | After ouabain: Maximum increase in contractile force (%) | After ouabain: Cardiac rhythm |
|---|---|---|---|---|---|---|---|---|
| *Normal dogs* | | | | | | | | |
| 1. | 160 | 11.0 | SR* | 80 | 240 | 50 | 36 | VT† |
| 2. | 140 | 7.0 | SR | 60 | 240 | 71 | 57 | VT |
| 3. | 140 | 9.5 | SR | 80 | 220 | 57 | 84 | VT |
| 4. | 200 | 10.0 | SR | 80 | 220 | 10 | 60 | VT |
| 5. | 160 | 11.0 | SR | 60 | 240 | 50 | 100 | VT |
| Mean | 160 | 9.7 | | 72 | 232 | 47.6 | 67.4 | |
| S.E. Mean‡ | ±11.1 | ±0.75 | | ±5.0 | ±5.0 | ±10.3 | ±11.3 | |
| *Reserpine-pretreated dogs* | | | | | | | | |
| 1. | 130 | 9.5 | SR | 80 | 200 | 54 | 58 | VT |
| 2. | 130 | 7.0 | SR | 80 | 220 | 70 | 157 | VT |
| 3. | 120 | 10.5 | SR | 80 | 220 | 83 | 100 | VT |
| 4. | 120 | 11.0 | SR | 100 | 200 | 67 | 45 | VT |
| 5. | 100 | 8.0 | SR | 100 | 200 | 100 | 75 | VT |
| Mean | 120 | 9.2 | | 88 | 208 | 74.8 | 87 | |
| S.E. Mean | ±5.6 | ±0.76 | | ±5.0 | ±5.0 | ±7.9 | ±20.1 | |

*SR: Sinus rhythm.
†VT: Ventricular tachycardia.
‡S.E. Mean: Standard error of mean.

## Results

*Control dogs.* Ouabain, 120 μg per kilogram in divided doses, caused a complete auriculoventricular block in one dog and resulted in an idioventricular rhythm that was followed by cardiac arrest. Ventricular tachycardia was produced in 5 dogs after cumulative doses of ouabain which ranged from 60 to 80 μg per kilogram. Ouabain also increased the myocardial force of contractions. The results are summarized in Table I.

*Reserpine-pretreated dogs.* Ouabain produced effects on the rhythm and contractile force of the heart in the reserpine-pretreated animals which were similar to the effects produced by ouabain in the control group. Cardiac arrest preceded by a 4 to 1 auriculoventricular block was obtained in one dog after a total dose of 140 μg per kilogram of ouabain. Ventricular tachycardia occurred in 5 dogs after cumulative doses of ouabain which ranged from 80 to 100 μg per kilogram were given. There was no significant difference ($0.02 < p < 0.05$) between the mean dose of ouabain required to establish ventricular tachycardia in the control animals and that in the reserpine-pretreated dogs. The mean increase in myocardial contractile force was greater in this group than in the control group; however, the difference was not statistically significant ($0.4 < p < 0.5$). The results are summarized in Table I.

*DCI-pretreated dogs.* Ventricular tachycardias which were of the same intensity, when judged by rate, as those in the control and reserpine-pretreated dogs were produced in dogs which were pretreated with DCI (5 mg. per kilogram intravenously). The dose of ouabain required to establish the arrhythmia ranged from 60 to 80 μg per kilogram. DCI was shown, prior to the injection of ouabain, to markedly reduce or abolish the positive inotropic and chronotropic effects of isoproterenol (1 μg per kilogram). A second injection of 5 mg. of DCI per kilogram was

made during the course of the ventricular tachycardia. The compound had little or no effect on the existing rate or rhythm of the heart in two tests. In one test, a bout of sinus tachycardia which lasted for less than 30 seconds was observed after the injection of DCI. This was not considered to be a significant change. DCI alone produced increases in the sinus rate and myocardial force of contractions. The maximum increases in the heart rate due to DCI in these 3 dogs were 16, 37, and 83 per cent of the control value, and the maximum increases in the myocardial contractile force were 17, 36, and 53 per cent of the control value.

## Discussion

The results of this study suggest that the mechanism by which ouabain causes ventricular ectopic beats in the anesthetized dog is not dependent on the release of catecholamines from the heart, adrenal medulla, or stores which mediate the response of adrenergic nerves to the heart and certain other sites. Ouabain, in essentially the same doses, produced ventricular tachycardia in the control group as frequently and of the same intensity, when judged by rate, as in dogs in which the heart, adrenal glands, and stores subserving the action of several adrenergic nerves have, presumably, been depleted of catecholamines by reserpine.[5-7] This suggestion is further supported by the fact that pretreatment of dogs with DCI, which has been reported to inhibit ventricular tachycardia caused by epinephrine or norepinephrine,[5] did not alter the frequency of appearance of ventricular tachycardia, in these tests, and did not diminish the rate of the ventricular tachycardias which were produced. Furthermore, the injection of DCI during the tachycardia had little or no effect on the arrhythmia. The results of the experiments utilizing DCI are, however, complicated by the fact that DCI alone possesses sympathomimetic actions on the heart, which were observed in these tests and reported by Moran and Perkins.[8]

The results also suggest that the increase in myocardial force of contractions produced by ouabain is not due, in part, to the release of catecholamines, as suggested by Cairoli and co-workers[1] and Tanz,[9] since the ability of ouabain to increase the myocardial force of contractions was not inhibited in dogs pretreated with reserpine; however, the experimental conditions between these tests and those of Cairoli and co-workers and Tanz are so widely divergent that any attempt at a possible explanation of this apparent discrepancy would be purely speculative.

## Summary

The findings reported in this study suggest that the increase in cardiac automaticity and the increase in myocardial contractile force due to ouabain are not dependent on the release of catecholamines from the heart, adrenal glands, or stores which mediate the response of certain adrenergic nerves.

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# Case reports

## Pulmonary atresia with intact ventricular septum
## Report of two cases
## studied by selective angiocardiography and right heart catheterization

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In 1956, Greenwold and collaborators[1] reported that cases of pulmonary atresia with intact ventricular septum could be divided into two groups: those in which a tiny or small right ventricular cavity (Type 1) was manifest, and those in which there was a right ventricular cavity of large or normal size (Type 2). They suggested that these two groups could be differentiated on the basis of roentgenographic and electrocardiographic data. Recently, Davignon and collaborators[2] reported on 20 cases, and further differentiated the two groups by means of similar criteria. They noted that in patients who are more than 1 week of age the correct diagnosis can usually be made on these grounds, but suggested that selective angiocardiography from the right ventricle should serve in doubtful cases to establish the diagnosis and differentiate the types with accuracy. We have recently studied 2 patients with pulmonary atresia and intact ventricular septum by means of catheterization of the right side of the heart and selective angiocardiography. One of these patients had a right ventricular cavity of small size, and the other had a large right ventricular cavity.

It is the purpose of the present report to describe these 2 cases in detail, emphasizing the hemodynamic and roentgenographic differences between the two types, as demonstrated by right ventricular angiocardiography and right heart catheterization.

### Report of cases

*Case 1.*† A 10-day-old white boy was hospitalized because of the history of a cardiac murmur and moderate cyanosis since birth. Cardiac enlargement had been noted on roentgenologic examination when he was 3 days old. The mother's pregnancy had been normal, and the family history was noncontributory.

Physical examination showed a well-developed, irritable white boy with Grade 2 (on a basis of 1 to 4) generalized cyanosis. No thrill was felt on palpation of the precordium. The second cardiac sound was thought to be single in the pulmonary area. A Grade 3 (on a basis of 1 to 4) continuous murmur was present, and was heard best at the upper left

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†This case was briefly referred to in a previous publication.[2]

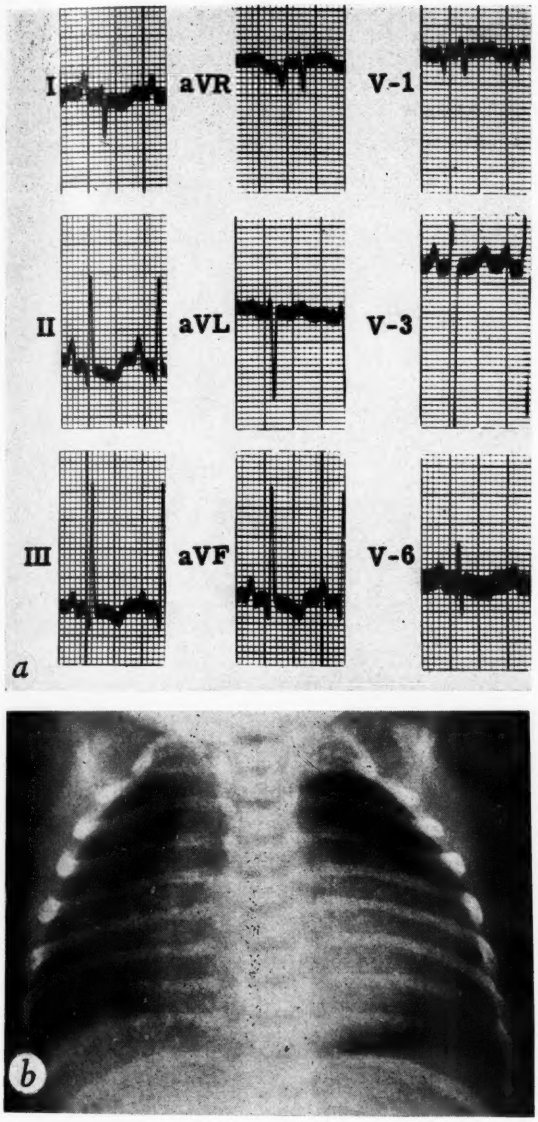



Fig. *1.* Case 1. *a*, Electrocardiogram made when the patient was 10 days old, showing evidence of right atrial enlargement and left ventricular dominance for this patient's age (see text). *b*, Anteroposterior thoracic roentgenogram, showing pronounced cardiac enlargement. Note unusual prominence of the border of right side of heart. Pulmonary vasculature is decreased.

sternal border; the systolic component appeared to be harsher, predominated at the apex, and extended toward the left axilla. The lungs were clear. The edge of the liver was palpable at the right costal margin. The femoral pulses were of good quality. The remainder of the physical examination was noncontributory.

The electrocardiogram showed alternating periods of sinus and nodal rhythm. The QRS axis was +100 degrees. The presence of peaked P waves indicated right atrial enlargement. The configuration of the QRS complexes in the standard and unipolar extremity leads as well as in the precordial leads indicated left ventricular dominance for an infant of this age. An interesting shift of the T axis in the frontal plane was also noted; the axis was −100 degrees, with inverted T waves in Leads I, II, III, and $aV_F$, and upright T waves in Leads $aV_R$ and $aV_L$ (Fig. 1,*a*).

A roentgenogram of the thorax showed cardiac enlargement with a prominent right border of the heart and decreased pulmonary vasculature (Fig. 1,*b*).

Four days after admission the patient was examined by means of combined right heart catheterization and angiocardiography. For this purpose a local anesthetic agent was administered, without premedication. The data on pressures and oxygen saturation of the blood obtained at that time are summarized in Table I. The systolic pressure in the right ventricle was higher than that in the femoral artery. The end-diastolic pressure in the right ventricle was normal. The right and left atrial pressures were similar in magnitude, and the contour of the right atrial pulse was normal. There was desaturation of femoral arterial blood which resulted from the presence of a large right-to-left shunt at the atrial level, as shown by the low saturation in the left atrium and by indicator-dilution curves. The oxygen capacity of the blood was 22 ml. per 100 ml.

Indicator-dilution curves were recorded at the femoral artery after injection of 5 mg. of Cardio-Green. Dye curve 1, recorded after injection of the indicator into the right ventricle, demonstrated an appearance time of approximately 5 seconds, a large initial deflection, and a very slow clearance of dye from the circulation. Dye curves 2 and 3, made after the injection into the inferior vena cava and left atrium, respectively, were similar to curve 1, except for the 3-second appearance times and more rapid build-up phases. These curves indicated the presence of a large right-to-left shunt, with the passage of dye to the pulmonary vascular bed occurring downstream to the left atrium. The dye injected into the right ventricle obviously cleared from this chamber with considerable rapidity, indicating that the blood in the right ventricle exchanged freely with the principal circulation. Study of the time components did not permit us to say whether exchange occurred backward through the tricuspid valve or forward through the abnormal myocardial sinusoids which were present.

*Table* I. *Hemodynamic data in Case 1 (small right ventricle—Type 1)*

| *Site* | *Pressure (mm. Hg)* | *Oxygen saturation** (%) |
|---|---|---|
| Femoral artery | 85/42 to 70/42 | 62 |
| Right ventricle | 130/4 to 13 | 42 |
| Right atrium, mid | 14/2† | 27 to 46 |
| Left atrium | 14/3† | 73 |
| Superior vena cava | — | 31 |
| Inferior vena cava | — | 24 to 43 |

*By cuvette oximeter. †"a" wave.

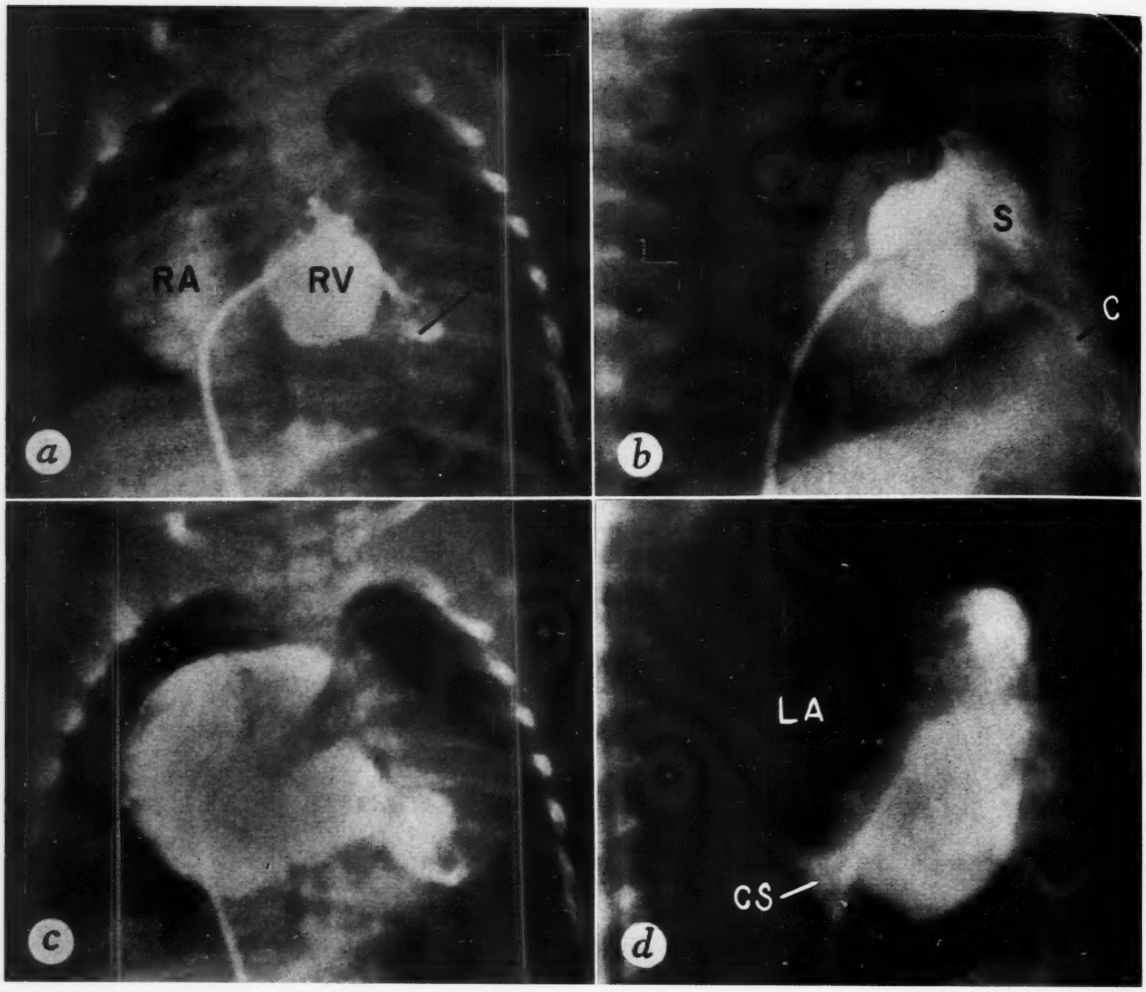



Fig. 2. Case 1. *a* and *b*, Angiocardiogram made with injection into right ventricle (*RV*). Catheter has rebounded so that some of the contrast medium has entered the right atrium (*RA*). Right ventricular cavity is extremely small. Myocardial sinusoids (*S*) are well visualized. Note the anomalous coronary vessel (*C*), which, at necropsy, was found to communicate with the myocardial sinusoids. *c* and *d*, Films made later in the same series. Tip of catheter has now rebounded completely into the right atrium. In lateral view the left atrium (*LA*) is now faintly opacified by way of the atrial septal defect. Reflux filling of coronary sinus (*CS*) from right atrium has occurred.

An angiocardiogram was made with the injection of 5 ml. of Ditriokon* into the right ventricular cavity in 1 second, without disturbance in cardiac rhythm. In both anteroposterior and lateral views a right ventricular cavity of small size could be seen clearly in the early films. Some opacification of the right ventricular wall was noted (Fig. 2); this resulted from filling of the abnormal myocardial sinusoids which occur in most cases of pulmonary atresia with intact ventricular septum of Type 1.[2] A pulmonary outflow tract or a pulmonary artery was not seen. After the first few films, and for the greater part of the injection, the catheter recoiled into the dilated right atrium. The left atrium was also visualized later. Contrast medium remained in the right ventricular cavity and in the myocardial sinusoids until the end of the series.

Because the locus of entry of the medium into the pulmonary artery could not be determined, a second angiocardiogram was made 30 min. later through the left atrium (Fig. 3), into which the catheter had been advanced through an interatrial communication. The same amount of opaque medium was injected in 1.5 seconds. The left atrial appendage retained contrast medium throughout the sequence. The left cavities of the heart were well visualized; the left ventricle appeared to be slightly larger than normal in diastole. The aorta was opacified, and this was followed almost immediately by opacification of the right and left pulmonary arteries; the pulmonary vessels were presumably filled through a patent ductus arteriosus, although this structure was never clearly visualized, possibly because of superimposition of the left atrial appendage. On none of the films could the main pulmonary artery be seen with certainty (Fig. 3),

*Contains sodium diprotriozoate (31 per cent) and diatrizoate (37 per cent).

A diagnosis of pulmonary atresia with intact ventricular septum was made, although the type was not specified. Because the condition of the infant was deteriorating rapidly, a Brock procedure was attempted the day after cardiac catheterization. Through a stab wound in the right ventricular wall, a steel probe was forced into the pulmonary artery and then a curved clamp was introduced and opened rather widely, with its tip in the pulmonary artery. Because of the small size of the heart, it was not possible to be absolutely certain of these various manipulations. At the completion of the procedure the heart action became slower and weaker, and progressed to a complete standstill, with no response to any of the usual resuscitative measures.

Necropsy revealed that the right atrium was extremely large. A patent foramen ovale was present, partially covered by a redundant remnant of the venous valves. The right ventricular cavity was small, and the right ventricular walls, which were extremely thick, contained numerous small sinusoids and a large anomalous vessel which originated near the apex of the heart and curved upward to anastomose with the anterior descending coronary artery (Fig. 4). The tricuspid orifice was small, and the leaflets of the tricuspid valve were somewhat thicker than normal, but there was no shortening of the chordae tendineae, and the valve appeared to be competent. There was no outflow tract from the right ventricle; its cavity terminated blindly, approximately 4 or 5 mm. below the atretic pulmonary valve. The pulmonary artery was about half the size of the aorta. The left ventricle was of good size, and the left cavities of the heart appeared to be normal. It was apparent that the surgical tract from the right ventricle had entered the left ventricle at the root of the aorta and had not entered the pulmonary artery as we had thought at the time of operation. The atretic pulmonary valve was intact. The ductus arteriosus was large and widely patent. Microscopic sections of the right ventricular wall showed a few regions of fibrosis scattered throughout the myocardium.

*Case 2.* A 1-day-old white boy was admitted to the hospital because he had had persistent cyanosis and a "fluttering heart" since birth. The mother's pregnancy had been normal, the delivery had been uncomplicated, and the birth weight of the child was 5 pounds 11 ounces (2,580 grams). Physical examination showed a small, active baby who was moderately cyanotic, but in no distress. No thrill was felt over the precordium. The heart sounds were of good quality. The second cardiac sound was thought to be single, and a Grade 4, harsh systolic murmur of long duration was heard along the left lower sternal border. A soft murmur of brief duration was heard in late diastole. The peripheral pulses were of good quality. The edge of the liver was palpated 2 cm. below the right costal margin; it was not pulsatile.

The electrocardiogram showed normal sinus rhythm. Extreme right axis deviation was present; the QRS axis was $-170$ degrees. The configuration of the P waves indicated atrial enlargement. The QRS complex was 0.10 second in duration, and indicated delayed activation of the right ventricle, which was consistent with dilatation of that chamber (diastolic or volume overloading). The left ventricular patterns were normal (Fig. 5,*a*).

A roentgenogram showed that the cardiac silhouette was considerably enlarged, especially in the region of the right atrium. The vascularity of the lungs was decreased (Fig. 5,*b*).

Because of increasing cyanosis and gradual deterioration of the patient's condition, a definitive diagnosis was considered necessary, and cardiac catheterization was undertaken the next day. The procedure, performed without anesthesia, was

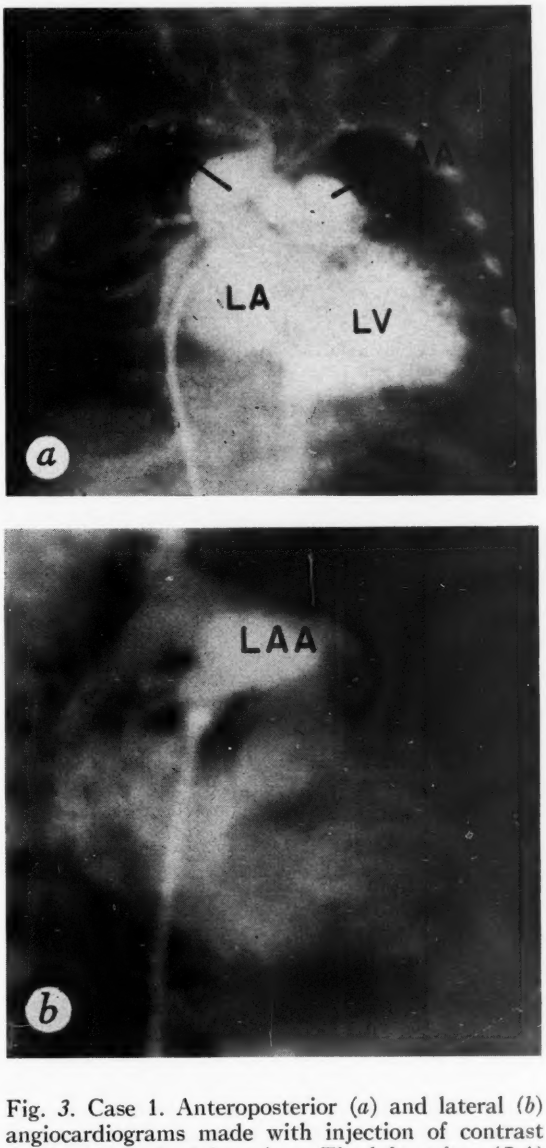



Fig. *3*. Case 1. Anteroposterior (*a*) and lateral (*b*) angiocardiograms made with injection of contrast medium into the left atrium. The left atrium (*LA*) and its appendage (*LAA*), the left ventricle (*LV*), and the ascending aorta (*Ao*) were opacified, in that order. Immediately after opacification of the ascending aorta the pulmonary arteries were opacified, presumably by way of a patent ductus arteriosus, although the ductus itself was never visualized, because of superimposition of the opacified left atrial appendage. Cavities of the left side of the heart are of normal size.

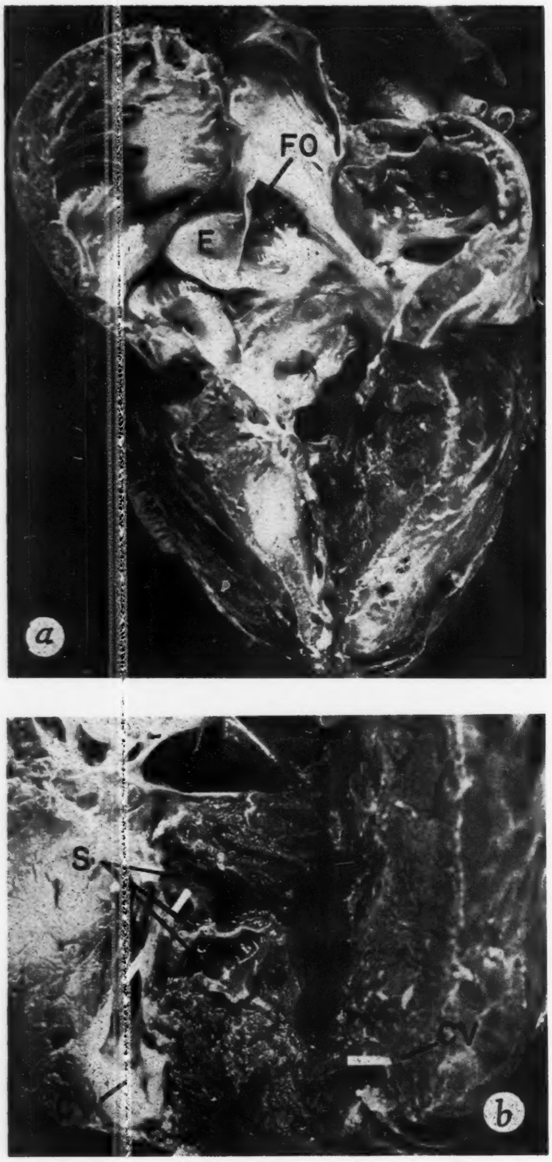



Fig. 4. Case 1. *a*, Right side of heart, showing large right atrium and small right ventricular cavity. One probe was passed from the left atrial side through the patent foramen ovale (*FO*). Another probe was passed from the inferior vena cava to the right atrium to demonstrate the large Eustachian valve (*E*). *b*, Close-up view of right ventricular wall, showing sinusoids (*S*) and anomalous coronary vessel (*CV*); probes are in apical portion of this vessel.

limited in scope. The data on pressures and oxygen saturation of the blood are given in Table II. The pressure tracing from the right atrium showed a prominent "v" wave, which was consistent with some degree of tricuspid regurgitation. The pressure in the right ventricle was normal for this chamber and was significantly less than that in the left ventricle; since pulmonary atresia was present, these pressures can be explained on the basis of severe tricuspid regurgitation or failure of the right ventricle. The oxygen saturation of blood from the left ventricle was approximately 40 per cent, but the degree of saturation of samples of blood drawn from the right side of the heart showed considerable variation, possibly because of the precarious cardiovascular condition of the patient.

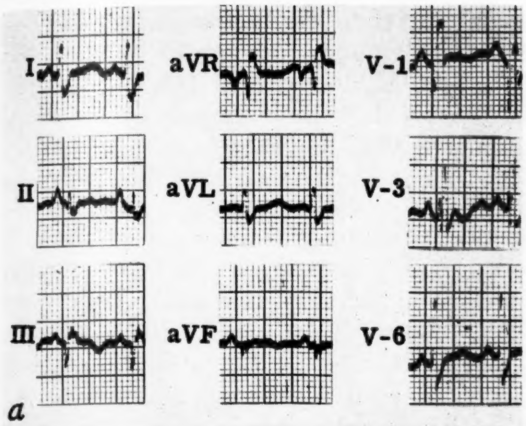
For the angiocardiogram, 4 ml. of Ditriokon was injected into the outflow tract of the right ventricle. The right ventricle was thin walled, enormously dilated, and occupied the greater part of the left portion of the cardiac silhouette. The right atrium filled from the right ventricle because of the presence of severe regurgitation through the tricuspid valve. This valve appeared to be situated more to the left than is normal. The right atrium and its appendage were also greatly dilated; the right atrial appendage occupied most of the heart shadow anteriorly and to the right of the spinal column. The right ventricle ended as a blind pouch directly under the position at which the pulmonary valve is usually seen. Neither the main pulmonary artery and pulmonary valve nor the left ventricle and left atrium were visualized (Fig. 6).

The diagnosis was pulmonary atresia with intact ventricular septum and a large right ventricle (Type 2).[2] A Brock procedure was carried out a few hours after the catheterization. The right atrium and right ventricle were greatly dilated. The great vessels were normally oriented. The main pulmonary artery was approximately half the size of the aorta. At its origin, the pulmonary artery narrowed to form a firm atretic vessel a few millimeters in length. A stab wound was made low in the right ventricle, and through this a pointed knife was inserted toward the pulmonary artery. On two occasions it passed through the obstructed segment into the pulmonary artery. A small Brock dilator was forced along the same pathway, but it was extremely difficult to be certain that the instrument had passed through the obstructed segment. Finally, a Potts basket dilator was passed into the heart, but when an attempt was made to force it into the pulmonary artery, the dilator emerged from the right ventricle adjacent to the pulmonary valvular ring, which

*Table* II. *Hemodynamic data in Case 2 (large right ventricle—Type 2)*

| *Site* | *Pressure (mm. Hg)* | *Oxygen saturation* (%)* |
|---|---|---|
| Femoral artery | Not entered | — |
| Left ventricle | 67/7 | 41 |
| Left atrium | 8†/−3 | 42 to 54 |
| Right ventricle | 28/8 | 20 to 28 |
| Right atrium, mid | 7‡/2 | 37 |
| Inferior vena cava | — | 29 |
| Superior vena cava | — | 17 |

*By cuvette oximeter.
†"a" wave.
‡"v" wave.



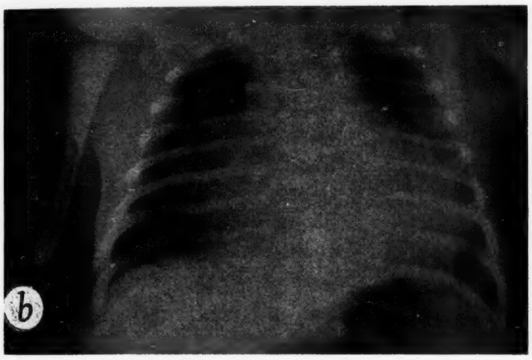



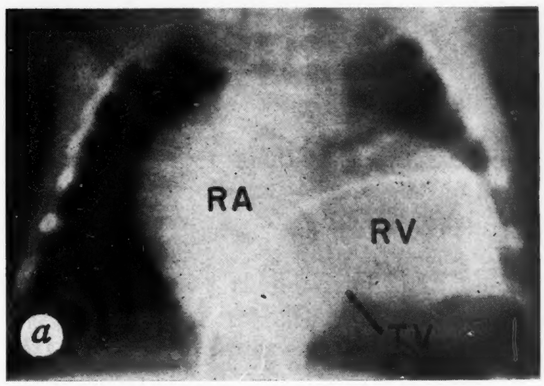

Fig. 5. Case 2. *a*, Electrocardiogram taken when the patient was 1 day old. Note large P waves and evidence of delayed activation of the right ventricle (see text). *b*, Anteroposterior thoracic roentgenogram, showing extreme cardiac enlargement with pronounced enlargement in the region of the right atrium. Pulmonary vasculature is decreased.

resulted in some bleeding. A suture closed this defect satisfactorily, but cardiac action deteriorated rapidly and finally ceased. All attempts to restore cardiac action failed. A postmortem examination was not made.

## Comment

In pulmonary atresia with intact ventricular septum the patients are usually severely ill, cyanotic infants. The great majority die before the age of 3 months. If the patients are more than 1 week of age, the two types of this cardiac defect can usually be differentiated on the basis of clinical, electrocardiographic, and roentgenographic findings.[2] Those infants with a right ventricular cavity of small size (Type 1) will, in general, show moderate cardiac enlargement on the roentgenogram of the thorax, and evidence of right axis deviation, left ventricular overload, and atrial hypertrophy on the electrocardiogram. Those with a right ventricular cavity of normal size or larger (Type 2) will show pronounced cardiac enlargement on the roentgenogram of the thorax, and evidence of right ventricular hypertrophy, right atrial enlargement, and right axis deviation with good, but not abnormal, left ventricular potential on the electrocardiogram. In our experience, these criteria usually do not apply to patients who are less than 1 week of age; in younger patients, the picture is atypical because the described roentgenographic and electrocardiographic features have not yet developed.

Hemodynamically, Type 1 and Type 2 cases are quite different. In cases of Type 1 the tricuspid valve, although small, is usually normally formed and appears to be competent. Once the blood is in the right ventricle, it has no ready path of egress and may be forced under high pressure



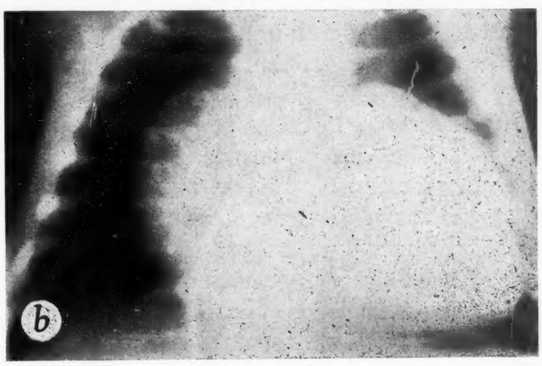




Fig. 6. Case 2. Angiocardiogram made with injection of contrast medium into right ventricle (*RV*). *a*, Ventricular systole. *b*, Ventricular diastole. Dense opacification of the right atrium (*RA*) has occurred because of the presence of tricuspid insufficiency. Right ventricular cavity is large. The tricuspid valve (*TV*) lies to the left of its usual position.

through abnormal myocardial sinusoids.[3] These sinusoids are thought to be persistent embryologic channels which have been kept open by the high right ventricular pressure which prevails throughout fetal and early postnatal life. They communicate by abnormal vessels with the coronary vascular system. The angiocardiogram in Case 1 suggests that the dye is forced through these myocardial sinusoids and from there, in a retrograde fashion, into the coronary circulation. Clearance of dye from the ventricular cavity is slow. Indicator-dilution curves are not specific. The observed prolongation of the time components of the right ventricular curve could have been the result of slowed clearance, either in a backward (via the tricuspid valve) or in a forward (via the sinusoids) direction. Militating against the presence of severe tricuspid insufficiency in Case 1 were the normal contour of the right atrial pressure and the presence of a pronounced elevation of right ventricular systolic pressure. It has been suggested recently that in these cases a regurgitant tricuspid orifice prevents the obstructed ventricle from becoming obliterated by stasis thrombosis.[4]

In cases of Type 2 the tricuspid valve is usually grossly malformed and obviously incompetent. The blood is driven back and forth across it during the cardiac cycle. Tricuspid insufficiency is the main factor in dilatation of the right ventricular cavity. In approximately half of the cases the appearance of the tricuspid valve resembles that seen in an Ebstein malformation. The leaflets are elongated and partially fused to the right ventricular wall or the ventricular septum. These facts are well demonstrated by the angiocardiogram in Case 2. The thin-walled large ventricular chamber is seen clearly, as is the evidence of gross regurgitation through the tricuspid orifice. The tricuspid valve is displaced more to the left than is normal. This image could well have been caused by the afore-mentioned malformation of the valve. The hemodynamic data were not remarkable in this case, except for the low right ventricular pressure, which is an obvious consequence of gross tricuspid insufficiency.

In cases of Type 1 the extent of the muscular obstruction in the atretic right ventricular outflow tract makes any attempt at surgical correction by means of a Brock procedure unlikely to succeed. Furthermore, the capacity of the small right ventricle may not be sufficient to accept a normal pulmonary flow, at least in the early postoperative phase; this would make a Brock procedure, even if technically successful, hemodynamically ineffective.

Creation of a Blalock or a Potts anastomosis would certainly seem to be the most effective way of providing the necessary flow of blood to the lungs in these cases. However, such procedures are technically difficult in small infants, and the usual precarious condition of these patients increases the hazard of any operation. In cases of Type 2 the large right ventricular cavity usually extends directly under the atretic valve; a thin membrane separates the ventricular cavity from a usually adequate pulmonary artery. In theory, at least, a Brock procedure is more likely to be successful in such a case. However, in the presence of the wide orifice of an incompetent tricuspid valve, the right ventricle may be incapable of building up enough pressure to force blood in significant quantity through the small opening created by the Brock procedure. In such cases an operation to provide a shunt may have a greater chance of success, but the problems posed by this group of cases are major ones. At present, direct visualization of the defect with the use of extracorporeal circulation would certainly seem to be the method of choice, but we have not attempted this type of treatment to date. Although these considerations do not induce an optimistic outlook with regard to surgical treatment, and the mortality due to operation in such cases has been extremely high, surgical intervention seems justified because of the natural course followed by patients with this malformation who are not treated surgically.

## Summary

Two cases of pulmonary atresia and intact ventricular septum have been presented. In one case a right ventricular cavity of small size was present (Type 1), and in the other a right ventricular cavity of large size was found (Type 2). The patient with the Type 1 defect had high right ventricular pressure and a normal

contour of atrial pressure. Injection of opaque medium into the right ventricular cavity demonstrated anomalous myocardial sinusoids. The patient with the Type 2 lesion had a normal right ventricular pressure and a dominant "v" wave in the contour of the right atrial pressure curve. An angiocardiogram showed a large, dilated right ventricular cavity, gross tricuspid regurgitation, and a tricuspid valve displaced to the left. The surgical implications of these findings were discussed briefly.

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# Acquired ventriculo-septal aneurysm with late spontaneous perforation of the septum

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Acquired cardiac aneurysms, whether atrial, ventricular, or septal, usually follow myocardial infarction.[1-3] Such aneurysms usually rupture through necrotic muscle within 2 weeks of infarction.[2-7] No reports of late rupture of ventriculo-septal aneurysms have come to our attention, although there are few well-documented reports of rupture of the left ventricular wall occurring as late as 3 months after infarction.[18,27] In the case to be described, rupture occurred through scar tissue after an interval of some years—a circumstance not encountered in several large series of reported cases.[8-17]

## Case report

The patient, a 46-year-old white man was first seen on May 19, 1959, because of shortness of breath, precordial discomfort, and palpitation. These symptoms began acutely on the day before admission while he was lifting a heavy load from his truck. He was seized with deep substernal pain, which was accompanied by nausea and marked sweating. He was examined by his family doctor shortly after this episode and was found to have a Grade 4 systolic murmur (Grades 1-4) and thrill over the entire precordium.

In 1951, he had experienced a severe attack of precordial pain which radiated down the left arm. He was confined to bed at home for about a month and was told that he had had a "heart attack." An electrocardiogram was not recorded. After recovery he went back to work as a truck driver and felt quite well, except for occasional attacks of chest pain brought about by lifting heavy loads or strenuous exercise. In 1953, he consulted his family physician because of this pain. Physical examination gave negative findings; his blood pressure was 140/80 mm. Hg. His heart and lungs were normal on fluoroscopic examination, and an electrocardiogram revealed changes compatible with an old diaphragmatic infarction. His chest pain was relieved by nitroglycerin.

In 1954, he underwent a physical examination for life insurance, and no abnormality was found. No electrocardiogram was recorded. In 1956, he fell from his truck and fractured his left humerus and was admitted to another hospital for surgical treatment of this fracture. General physical examination gave negative findings. During the year 1958, he experienced mild exertional dyspnea, palpitation, and angina on exertion, but these symptoms did not interfere with his work. In January of 1959, he was hospitalized for 48 hours for removal of a metal plate from the left arm which had been inserted 3 years previously for reduction of the fractured humerus. Physical examination gave normal findings, apart from mild hypertension (blood pressure of 158/100 mm. Hg). No cardiac murmurs were heard.

*Physical examination* (*May 19, 1959*). The patient was a heavily built man in no acute distress. His blood pressure was 116/70 mm. Hg, pulse was 110 per minute, and respirations were 18 per minute. His temperature was 100°F. The apical impulse was palpable a little beyond the mid-clavicular line and was formed by a hypertrophied left ventricle. A systolic thrill was felt maximal in the fourth left intercostal space, and a Grade 4 systolic murmur was present over the same area. Râles were heard at both lung bases. The liver and spleen were not palpable. There was no peripheral edema.

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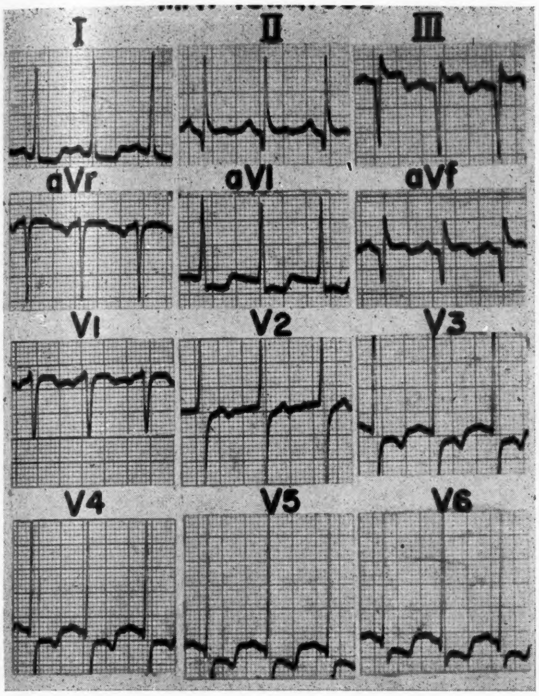


Fig. *1*. Electrocardiogram of May 19, 1959, shows abnormal Q waves and S-T and T-wave changes in Leads I, II, III, and $aV_F$ diagnostic of diaphragmatic myocardial infarction. Tall R waves in Leads I and $aV_L$, and over the left precordium are compatible with left ventricular hypertrophy.

An electrocardiogram taken on admission (Fig. 1) showed tall R waves in Leads $V_5$ and $V_6$, with S-T-segment and T-wave changes in the left precordial leads compatible with left ventricular hypertrophy and strain. In addition, changes consistent with diaphragmatic myocardial infarction were present in Leads II, III, and $aV_F$.

A chest x-ray film (Fig. 2) revealed some over-all increase in the size of the heart, with left ventricular enlargement and changes indicative of passive congestion in both lung bases.

Urinalysis was negative. The hemoglobin was 12.8 Gm. per cent, and the white blood cell count was 11,100 with 70 per cent neutrophils. The erythrocyte sedimentation rate was 24 mm. in one hour (Wintrobe). The blood urea nitrogen was 35 mg. per cent, and the blood sugar was 85 mg. per cent. Blood culture was negative, and the Eagle flocculation test for syphilis was also negative.

*Subsequent course*. He was put to bed, digitalized, given Diuril, and a low-salt diet. He improved considerably on this regimen and was discharged on June 1, 1959, receiving digitalis and 500 mg. of Diuril daily. Electrocardiograms on the second and twelfth days after hospitalization revealed no essential change from the tracing recorded at the time of admission.

At home he deteriorated rapidly. He became short of breath and developed edema of the legs and ascites. Because he developed nausea and vomiting, digitalis was discontinued. Two weeks after discharge, jaundice was first noticed and this gradually became worse. Palpitation became more severe and he began to complain of angina at rest.

The patient was readmitted to hospital on July 6, 1959. Physical examination revealed marked jaundice and orthopnea. The neck veins were grossly distended. Respirations were labored at a rate of 38 per minute. The blood pressure was 158/100 mm. Hg., and the arterial pulse was 100 per minute and irregular; the temperature was normal. There were signs of pleural effusions at both lung bases, and moist râles were heard bilaterally. The cardiac findings were unchanged from those at the time of the previous hospitalization. The abdomen was protuberant, and ascites was present, together with gross edema of legs, sacrum, and scrotum.

An electrocardiogram (Fig. 3) revealed a general decrease in amplitude of the QRS complexes over the left precordium and numerous premature ventricular beats. The changes in Leads II, III, and $aV_F$ were again compatible with an old diaphragmatic myocardial infarction. A chest x-ray film taken a week after admission revealed a further increase in the size of the heart, together with elevation of the right dome of the diaphragm consistent with hepatomegaly.

*Pertinent laboratory results*. The white blood cell count was 15,000 with a normal differential. The blood urea nitrogen was 138 mg. per cent. SGOT was 14 units. Serum bilirubin was 3.0 mg. per cent (direct, 1.8 mg.), plasma albumin 4.1 Gm., and globulin 2 Gm. Alkaline phosphatase was 6.2 Bodansky units. Thymol turbidity was 4.5 units. The serum sodium was 125 mEq. per liter, chloride 90 mEq., potassium 3.9 mEq., and the carbon-dioxide combining power 25 mEq. per liter.

Although he showed slight initial improvement after intensive treatment for congestive heart failure, he soon became refractory to such treatment and died 26 days after admission.

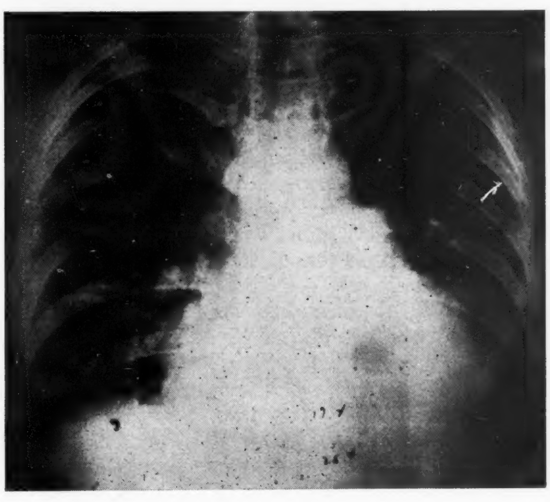

Fig. *2*. The chest x-ray film reveals changes indicative of passive congestion in both lung bases, with over-all increase in heart size and left ventricular enlargement.

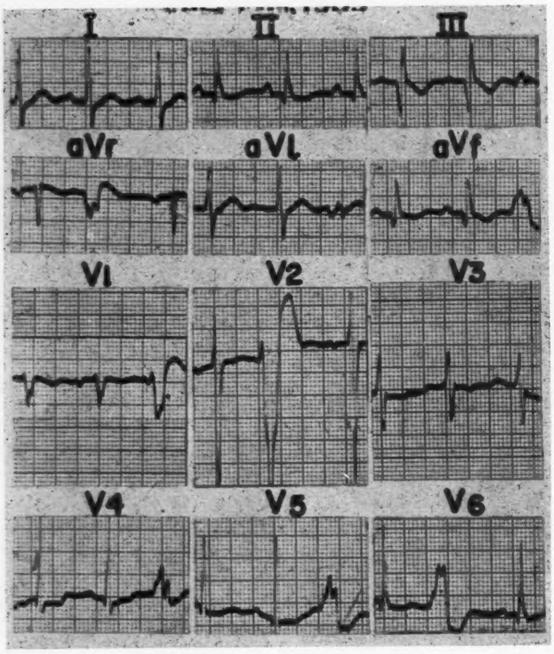


Fig. *3*. Electrocardiogram of July 17, 1959, shows the appearance of numerous premature ventricular beats and generalized decrease in amplitude of the QRS complexes.

*Necroscopy report.* Gross examination revealed bilateral pleural effusions, pericardial effusion, and ascites.

The heart weighed 575 grams. On the posterior surface of the left ventricle near the mitral valve (Fig. 4) was a thin-walled aneurysmal sac which was 3.5 cm. in diameter and 2 mm. in thickness. The left ventricle elsewhere measured 13 mm. in thickness. In the upper third of the interventricular septum (Fig. 5) was an acquired interventricular septal defect which measured 1.8 cm. in diameter. The edges were smooth and were surrounded by dense scar tissue. The area of myocardial scarring around the septal defect was continuous with the wall of the cardiac aneurysm. A mural thrombus was attached to the wall of the right atrium. There was complete occlusion of the right coronary artery, 5 cm. beyond its ostium, by organized thrombus. Elsewhere the branches of the right coronary artery contained large arteriosclerotic plaques which almost occluded the lumen. The left coronary artery and its branches were patent.

*Microscopic examination.* Multiple sections of the heart revealed extensive areas of fibrosis, most marked subendocardially. No evidence of inflammation or recent infarction was noted. Sections of the occluded right coronary artery revealed recanalized sclerotic thrombus, with no fresh clot. The edge of the interventricular septal defect and the wall of the aneurysm were formed by dense scar tissue.

## Discussion

Two of the serious complications which may result from acute myocardial infarction are rupture of the heart and formation of an aneurysm.

Rupture of the heart occurs in about 10 per cent of the patients with myocardial infarction,[3,4] and in 1 to 2 per cent such a rupture occurs through the ventricular septum.[4,8] The incidence of aneurysm after myocardial infarction is generally reported to be about 10 per cent.[18,22,26]

Rupture of the heart, whether through the septum or the ventricular wall, occurs through areas of myomalacia cordis and usually happens within 2 weeks of infarction.[4,8] Not infrequently the necrotic area forms an aneurysmal dilatation, and it is through this dilatation that rupture occurs. Rupture is very rare[1,3,4,6] once scar tissue has developed completely (some 3 months after the infarction).[5] In various large reported series of cardiac aneurysms, late rupture is not listed as a cause of death.[19-24,28] With regard to acquired ventricular septal defects,[8-10,12-17] rupture takes place through necrotic muscle, whether accompanying acute aneurysmal dilatation is present or not.

The case described presents the unusual feature of perforation of the septal part of a chronic ventriculo-septal aneurysm through scar tissue 8 years after the original

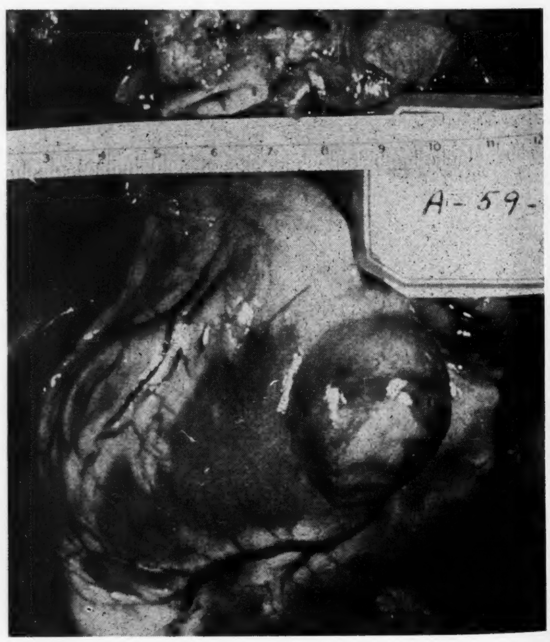


Fig. *4*. Photograph of the diaphragmatic surface of the heart, showing the ventricular part of the aneurysm bulging at the base of the left ventricle.

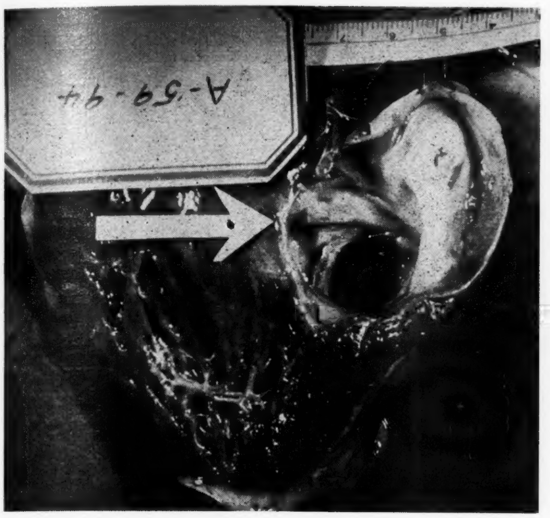

Fig. 5. Shows the entire ventriculo-septal aneurysm and perforation as viewed from the left ventricular cavity.

infarct, with no clinical or pathologic evidence of more recent infarction.

Anticoagulants, persistent elevation of the blood pressure after infarct, and early physical activity are factors which are believed to increase the incidence of cardiac rupture.[2,4] In this instance the onset of symptoms referable to septal perforation occurred during severe physical exertion. The blood pressure of the patient on one occasion only was recorded as 158/100 mm. Hg, but this degree of hypertension seems to be insufficient to have played a part in the cardiac rupture, although it might have had some bearing on the formation of the aneurysm.

Survival after septal perforation which follows myocardial infarction is, on the average, 7.4 days,[8] although there have been exceptional cases of long survival.[11] The patient reported upon here survived 10 weeks from the apparent time of septal perforation.

Finally, an unusual feature of the case described is the development of a ventriculo-septal aneurysm after occlusion of only the right coronary artery; the left coronary artery remained patent. This suggests that the distribution of the branches of the coronary arteries in this patient may have been unusual.

## Summary

The clinical and pathologic findings are presented from a patient with an acquired ventriculo-septal aneurysm and rupture of the interventricular septum. The unusual features of the case are: (1) rupture of the septum through scar tissue 8 years after the original infarct, (2) relatively long survival, (3) lack of correlation between the location of the aneurysm and the actual coronary pathology found at necroscopy, indicating, perhaps, an unusual distribution of the coronary artery branches.

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# Clinical pathologic conference

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## Clinical abstract

This 20-year-old Negro woman was admitted to the Charity Hospital of Louisiana on May 7, 1959, for cardiac operation.

The patient was first seen in 1956. She had been well until approximately 3 years before, when she noted easy fatigability and inability to play as heartily as her schoolmates. These symptoms began gradually over a period of several weeks to months. At that time she developed shortness of breath after only very moderate exertion. Her symptoms were very mildly, but definitely, progressive from the time of onset. There were no previous symptoms suggestive of rheumatic fever, and there was no history of previous cardiac examinations.

The physical and laboratory findings in 1956, and during the 3 years that she was followed in the outpatient cardiac clinic, were as follows. Blood pressure in the arms was 95/70 mm. Hg. Physical examination gave essentially negative findings except for the heart. The point of maximal impulse was in the fifth intercostal space, 2 cm. lateral to the mid-clavicular line. There was an extremely loud, harsh "diamond-shaped" systolic murmur loudest in the aortic area, but also heard in the neck, at the apex, and over the left posterior thorax. There was a loud pulmonic second sound which was not split. An electrocardiogram showed marked left ventricular hypertrophy (Fig. 1). Fluoroscopy and chest x-ray films revealed 3 to 4+ left ventricular enlargement, and questionable right ventricular enlargement (Fig. 2). The aorta was small and difficult to identify. The pulmonary segment was normal. There was no definite atrial enlargement. The easy fatigability of the patient continued to progress, but there were no symptoms suggestive of congestive heart failure.

In January, 1957, a blowing diastolic murmur was noted at the base and a third heart sound at the apex with a diastolic rumble. There was no accentuation of the first heart sound and no opening snap. In March of that same year the patient was found to be anemic, and in view of the changing murmurs a diagnosis of subacute bacterial endocarditis was considered. However, numerous blood cultures were negative. The anemia, which was later attributed to bleeding of the gums due to poor dental hygiene, responded slowly but significantly to oral iron therapy. The patient was maintained during the next 2 years on penicillin for prophylaxis of rheumatic fever.

In February, 1959, cardiac fluoroscopy was repeated specifically to search for calcification of the aortic valve; however, none was seen. In March, 1959, right and left heart catheterization was performed. A systolic gradient of approximately 100 mm. Hg across the aortic valve was demonstrated when the catheter was pulled back from the aorta into the left ventricle. The operator was of the opinion that the changes in pressure probably represented aortic valvular stenosis without subaortic stenosis. No significant diastolic gradient across the mitral valve was detected. Because of the severe left ventricular hypertrophy and progressive symptomatology, it was decided to attempt to correct the lesion surgically.

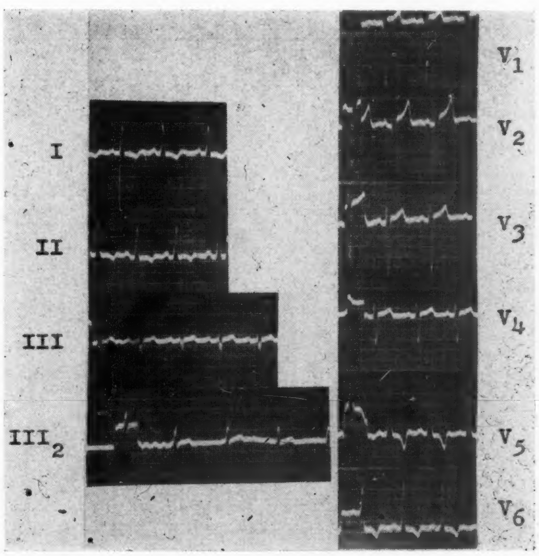


Fig. *1*. Electrocardiogram ($III_2$ is Lead III taken during deep inspiration).

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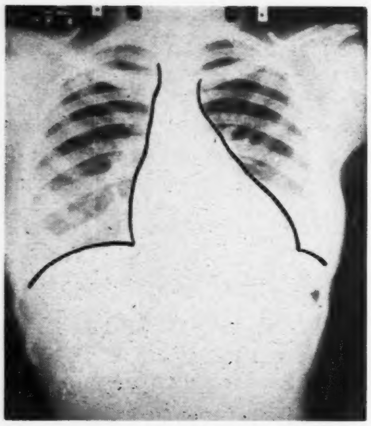

Fig. *2*. Erect posteroanterior x-ray view of the chest. Cardiac silhouette outlined.

The blood pressure at the time that the patient was last hospitalized was 100/60 mm. Hg. The remainder of the physical examination gave negative findings except for the examination of the heart which showed a normal sinus rhythm, absent aortic second sound, and a loud, harsh "diamond-shaped" systolic murmur over the aortic area accompanied by palpable thrill. A very soft, high-pitched diastolic blowing murmur was again heard at the base, but no apical rumble was detected.

*Hospital course.* On May 21, 1959, an open-heart operation with extracorporeal circulation was performed. The pump-oxygenator was used for about 30 minutes, and the patient seemed to tolerate this well. After the procedure, however, bleeding began at many sites, and the blood pressure fell. A test for activation of fibrinolysin was positive. She was treated by infusion of l-norepinephrine, and received a total of 30 Gm. of fibrinogen and 50 mg. of prednisolone intravenously over a period of several hours. In an attempt to replace the extensive loss of blood, a total of 30 pints of blood was given in the operating room. Although the bleeding never stopped completely, the thorax was closed and the patient was sent to the recovery room. Upon her arrival there the peripheral pulse could not be detected, and the blood pressure could not be measured. The heartbeat was regular. Several hours later, signs of pulmonary edema appeared and the patient died.

## Clinical discussion

DR. LOVE: There are two important aspects of this patient's illness. The first is the primary diagnosis, and the second is the cause for her failure to survive operation. This seems to be a straightforward case of aortic stenosis, but we must look for clues to other possible lesions.

The patient first began having symptoms at the age of 14 years, when she noted that she was unable to keep up with her playmates and was more easily fatigued. The onset of the fatigability was said to be gradual over a period of several weeks to months. This makes it seem genuine. She noted shortness of breath after very moderate exertion. This is not a common early sign of disability caused by aortic stenosis. Syncope on exercise is common, but real dyspnea is more suggestive of the onset of congestive heart failure, which is usually

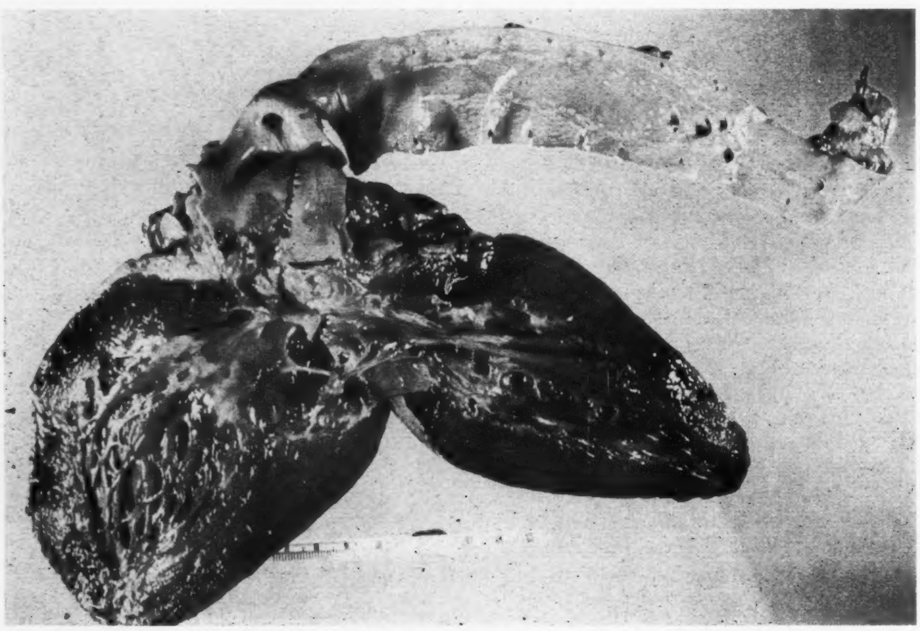

Fig. *3*. Interior view of left ventricle and aorta, showing the recent surgical incision and the aortic valvular and subvalvular stenosis (*arrow*).

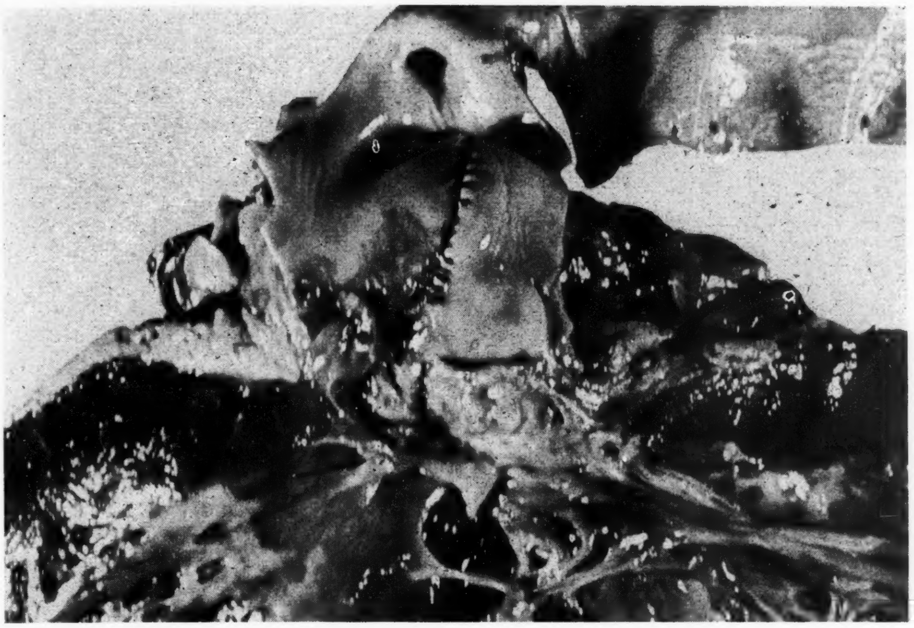

Fig. 4. Close-up view of left ventricle and aortic valve, showing the valvular and subvalvular stenosis (*arrow*).

a comparatively late manifestation. Her symptoms were definitely progressive. Therefore, this was not a static or trivial lesion, but one which produced significant and increasing disability. In 1956, the blood pressure was 95/70 mm. Hg, which is an extremely low pulse pressure, and it is difficult to accept this as being truly representative of the usual situation over that 3-year period. Most patients with aortic stenosis do not have such a low pulse pressure except during the terminal phases of their illness. We can ask ourselves whether the growth and development of this patient would have been normal if she had had congenital aortic stenosis since early infancy. The answer is yes. In collected groups of patients the degree of physical development was found to be essentially normal in most cases of uncomplicated congenital aortic stenosis.[1,2] There was a loud, harsh "diamond-shaped" systolic murmur heard best at the aortic area, but radiating into the neck and to the apex. This is, of course, typical of aortic stenosis. A loud pulmonic second sound was heard. This is difficult to evaluate. Why should there be a loud second sound to the left of the sternum? Was it because the aortic second sound was soft, or because of some coincident disease?

The first electrocardiogram in 1956 showed that marked left ventricular hypertrophy was already present at that time. Over the course of 3 years there were only minor changes in the tracings. I don't see anything in the electrocardiogram to suggest right ventricular hypertrophy. Fluoroscopy


Fig. 5. View of mitral valve area, showing the thickened and fused chordae tendineae.

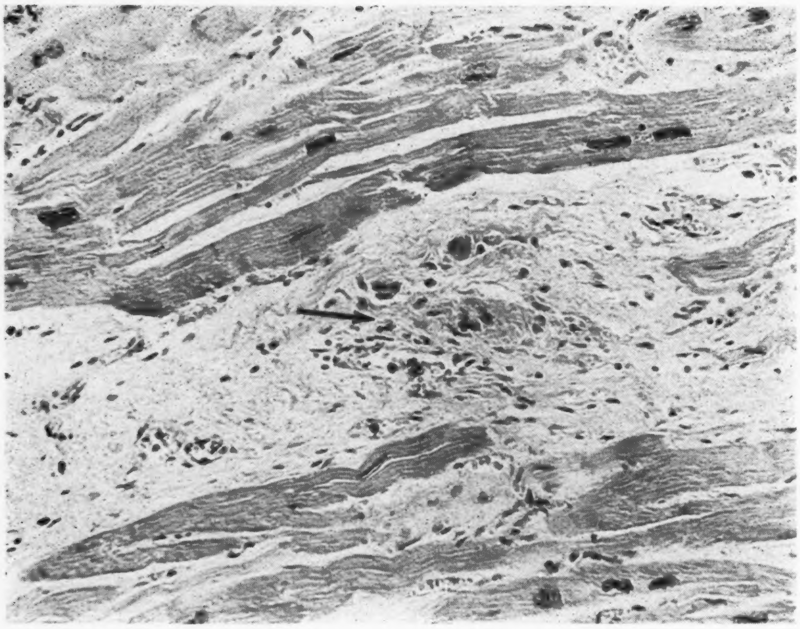

Fig. *6*. Photomicrograph of left ventricular myocardium, showing myocardial hypertrophy, interstitial fibrosis, and an Aschoff body (*arrow*).

revealed 3 to 4+ left ventricular enlargement and a slight anterior bulge of the right ventricle. Right ventricular enlargement, a loud pulmonic second sound, and the murmur suggestive of mitral stenosis which was heard later would go together well, but a slight anterior bulge of the right ventricle in the presence of a massive left ventricle is an uncertain sign indeed, since the left ventricle dominates the heart shadow and the right ventricle is but a small appendage on its anterolateral surface. The aortic knob was said to be small and hard to identify. The aortic knob in aortic stenosis is characteristically small. Another common roentgenologic finding which is not mentioned in the protocol is a dilatation and anterior prominence of the ascending part of the aorta. This is the most consistent fluoroscopic finding in aortic stenosis.[1] The pulmonary segment was normal, and there was no atrial enlargement. These findings would certainly be unusual in mitral stenosis and also in mitral insufficiency, which is another possibility. The patient's symptoms of fatigability continued to progress, but there were no definite symptoms of congestive heart failure. There was no angina or syncope on effort. These are two very common and ominous symptoms in aortic stenosis. In January, 1957, it was noted that there was a high-pitched, decrescendo diastolic murmur at the base. Such a murmur would usually originate from the pulmonary or aortic valve. Presumably, it was from the aortic valve in this case, although it could have been due to pulmonic insufficiency caused by mitral stenosis. There was a third heart sound at the apex with the diastolic rumble. We would need to know the exact timing and character in order to evaluate it. It could have been a normal third heart sound, a gallop, an opening snap, or, if systolic, an ejection click. The latter is heard at the apex in many patients with mild aortic stenosis. In March of that same year it was noted that the patient was anemic.

This might have been the cause of the diastolic apical rumble which was described. In February, 1959, cardiac fluoroscopy was carried out to look for calcification in the aortic valve, since the patient was in the age group in which calcium often begins to be deposited in the abnormal aortic valve; however, no calcification was seen. In the younger age groups, calcification is unusual, whatever the etiology. When patients reach 30 years of age, a majority have calcium in the valve whether the lesion is congenital or rheumatic. In

any case, no calcium was seen in this valve. In March, 1959, a maximal systolic gradient of about 100 mm. Hg was demonstrated to exist "across the aortic valve," establishing the presence of some type of obstruction in the outflow tract. Physical examination on the last admission showed an absent aortic second sound. Statistically, this is an unusual finding in aortic stenosis,[1,3] although it is a traditional belief that the aortic second sound is absent in this lesion. This is essentially all of the data available, and we will try to make a preoperative diagnosis. The diagnosis of mitral stenosis will have to be eliminated because there was no good clinical evidence to support the diagnosis, and because no gradient between the left atrium and the ventricle was detected at catheterization. There are a number of different anatomic conditions which could produce the drop in pressure in the aortic area, and it would be helpful to the surgeon to know which one he might be called upon to deal with. The stenosis may be in the aorta above the normal valve; this is rare.[4] It may be valvular, which is the most common type. It may be below the valve in the ventricle; this is not uncommon, and occurs in approximately 20 per cent of the patients with congenital aortic stenosis.[2,3] Another rare syndrome which has been described is that of muscular stenosis of the left ventricular outflow tract.[5] This lesion is particularly important to the surgeon, since all of the signs of aortic stenosis may be present; yet, in the heart, quiet at operation, a finger can be readily introduced through the aortic valve into the apex of the ventricle. The stenosis is presumably caused by a functional ring produced by the contraction of the ventricular muscle during systole. Our differential diagnosis rests primarily between valvular and subvalvular aortic stenosis. Another possibility is bicuspid aortic valve. This produces a systolic murmur and frequently a diastolic murmur, but it does not alone produce this type of ventricular hypertrophy. It is not ordinarily a very significant lesion from a dynamic point of view. Another possibility is mitral insufficiency. It is not always possible to distinguish between the murmurs of mitral insufficiency and those of aortic stenosis, particularly when the two coexist. The murmur of aortic stenosis may resemble the murmur of mitral insufficiency when the aortic second sound is delayed and the pulmonary second sound comes at the end of the aortic systolic murmur.[3] The differentiation between valvular and sub-

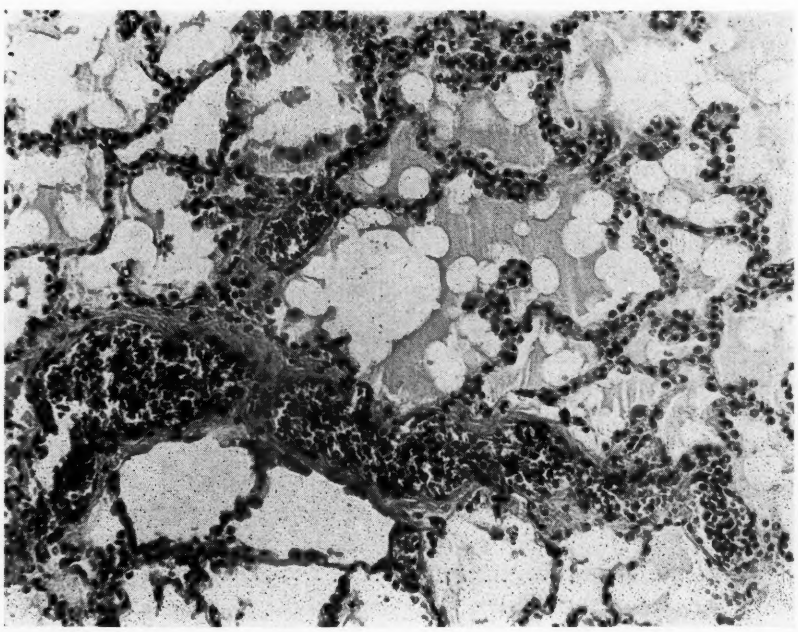

Fig. 7. Photomicrograph of lung, showing pulmonary thrombi. The thrombi are very cellular.

valvular aortic stenosis is impossible from the data available. One might reason that in a patient with a diastolic murmur the lesion must be in the valve itself. This is correct, but the process in subvalvular stenosis may also involve the valve producing a diastolic murmur. The degree of poststenotic dilatation in the aorta is of no value in the differentiation. The location and character of the murmur is also of no help. I will not try to distinguish between valvular and subvalvular stenosis, nor will I try to distinguish between rheumatic and congenital origin. However, we should remember that isolated rheumatic aortic stenosis would be unusual in a young woman.

The operative complication was manifested primarily by bleeding. The pathogenesis of hemorrhagic diatheses after operation and extracorporeal circulation is still obscure, even though techniques have been worked out which make this complication rare. A number of possible causes have been listed.[6] One is the incomplete neutralization of the heparin which is given at the time the patient is put on the pump. Surprisingly small amounts of heparin are used, however, i.e., 100 or 200 mg., so that this is probably not important. About three quarters of the platelets are lost in these pumps, but this is not believed to be a primary cause of the hemorrhagic tendency. The normality of the surviving platelets should be established. The activation of a fibrinolysin is not uncommon and apparently occurred in this patient. This can be detected by allowing the blood to clot and finding that the clot almost immediately dissolves. Certain essential factors, such as prothrombin or accelerator globulin, can be denatured by enzymes during the procedure, or coagulation can occur in the machine which consumes the prothrombin or other elements. Still another possibility is the loss of capillary tone which makes the patient resemble one with pseudohemophilia, that is, the blood will clot in the tube normally, but the bleeding from the cut surfaces will not be controlled. Although the patient received 30 Gm. of fibrinogen, or about twice the normal circulating body content, and a total of 30 pints of blood during the operative period, her bleeding was not controlled.

DR. LOVE: *Clinical diagnosis.* (1) Aortic stenosis. (2) Postoperative hemorrhagic diathesis, due in part to activation of a fibrinolysin.

## Pathologic discussion

DR. REED: At the time of autopsy the patient weighed 148 pounds and her body length was 160 cm. There was a recent vertical incision over the sternum that measured 23 cm. in length. When the body cavities were opened, there were 300 c.c. of bloody fluid in the peritoneal cavity, 400 c.c. in the right pleural space, and 200 c.c. in the left pleural space. The heart weighed 550 grams. There was marked left ventricular hypertrophy and dilatation, and slight right ventricular hypertrophy, with very little dilatation. The leaflets of the mitral valve were thickened, with shortening and fusion of the chordae tendineae, compatible with a healed rheumatic valvulitis. There was a valvular aortic stenosis which had been partially corrected by operation. The valve cusps were rigid and there was fusion of the cusps. The aortic valve ring measured 4.5 cm. in circumference. In addition, there was a subvalvular stenosis of a very significant degree. A somewhat trabeculated intimal fibrous plaque was present in the aorta immediately above the aortic valve. The pulmonic valve was scarred and thickened and showed some fusion of the cusps compatible with a healed valvulitis. The tricuspid valve was not remarkable. The left lung weighed 450 grams, and the right lung, 550 grams. There was marked congestion and edema. The spleen weighed 200 grams and was congested. The liver was also congested. There were multiple mucosal petechiae throughout the gastrointestinal tract. The brain was congested; it weighed 1,400 grams. Fig. 3 shows a view into the left ventricle of the heart, which was opened along the junction of the interventricular septum and the wall of the left ventricle. It is laid open to visualize the septum and the aortic valve. A rigid fibrous band can be seen completely encircling the aortic vestibule (arrow). This represents the subvalvular stenosis. There is also thickening of the aortic cusps, and immediately cephalad to the

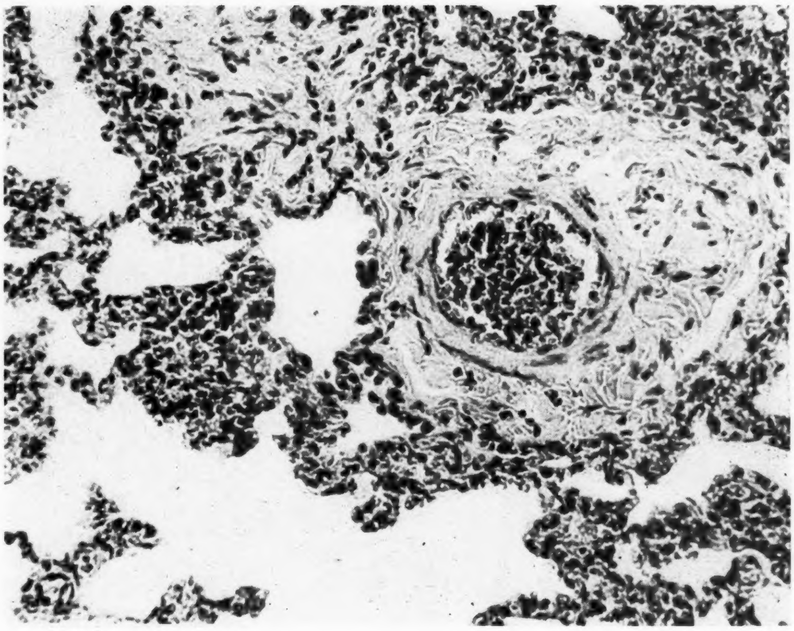

Fig. 8. Photomicrograph of pulmonary vessel, showing occlusion of the lumen by a cellular thrombus.

aortic ring there is a slightly roughened plaque which extends into the anterior aortic sinus. The recently sutured incision is seen beginning beside the plaque and extending cephalad. Fig. 4 is a close view of the aortic ring, showing the subvalvular stenosis (arrow) and the scarred and fused aortic cusps. Fig. 5 also shows part of the left ventricle, including the mitral valve. The valve leaflets are opaque, and the chordae tendineae are thickened and fused, giving a picture compatible with healed rheumatic valvulitis. There is also some thickening and opacity of the endocardium of the left atrium, suggesting a healed mural endocarditis. Fig. 6 is a photomicrograph of the myocardium. There is variation in the size of muscle fibers, with nuclei that are enlarged and irregular in shape, compatible with hypertrophy of the myocardium. There is a striking and diffuse increase in interstitial fibrous tissue throughout the left ventricle. In addition, one small Aschoff body (arrow) is present which contains characteristic Aschoff cells. This is good evidence of a recently active rheumatic myocarditis. Fig. 7 is a photomicrograph of a section of lung and demonstrates the probable cause of death and possibly the cause of generalized bleeding. An abundance of small recent thrombi are scattered diffusely throughout all sections examined. The thrombi are located, for the most part, in the lumina of small and medium-sized arteries. They are composed predominantly of leukocytes, but some fibrin is present in all instances. The fibrin can be identified sometimes in scattered individual clumps, but regularly in the form of delicate networks extending between the formed elements of the clot. The cause of this remarkably diffuse thrombosis of the pulmonary vessels is not apparent, but its effect could scarcely fail to be a severe depletion of circulating fibrinogen. It is probable that much of the fibrinogen administered to the patient was promptly fixed in the pulmonary thrombi and failed to reach the systemic circulation. Fig. 8 shows thrombi in the pulmonary vessels, and also shows fairly prominent pulmonary congestion. The vessels are somewhat thickened and show adventitial fibrosis. Fig. 9 is a high-power view that shows the endothelial swelling, which is very prominent in some sections, and the fibrillar material representing fibrin. The renal glomeruli present an interesting finding (Fig. 10). There are dilated glomerular capillaries which are completely bloodless, and a fat stain on these reveals that there has been fat emboli-

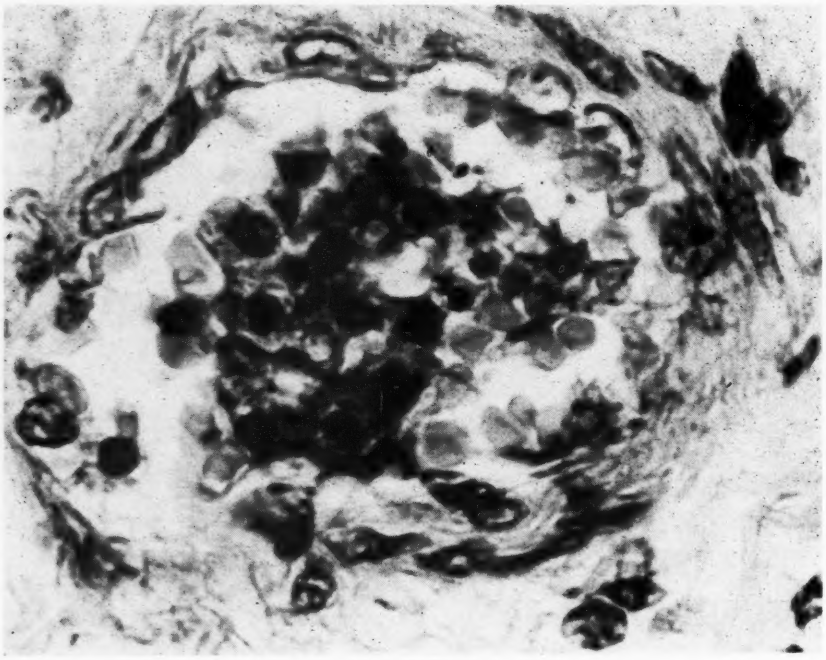

Fig. 9. Photomicrograph of a pulmonary vessel showing endothelial swelling and a thrombus with a poorly formed fibrin network.

zation. These emboli do not occur in great numbers but are easy enough to find. As a result of this finding, fat stains were done on sections of lung, and here, too, fat emboli are present.

In summary, this patient has several lesions. She has both valvular and subvalvular aortic stenosis. The subvalvular lesion is generally considered to be congenital and is sometimes associated with congenital aortic stenosis. It would be difficult to rule out congenital origin in this case. However, the patient has definite evidence of fairly extensive rheumatic heart disease, with both a myocarditis and valvulitis. Therefore, I think it is very likely that the aortic valvular stenosis had a rheumatic basis. An inflammatory basis for the subaortic stenosis, as well, cannot be excluded.[7] In addition, there are extensive pulmonary thrombi. I don't know why they formed. Neither do I know whether the clinical shock preceded or followed the intrapulmonary thrombosis. There may have been some local condition in the lung that favored coagulation of blood and the sequestration of fibrin. Certain experiments on intractable shock may explain in part the coagulation of the blood in the lungs[8-10] and the subsequent appearance of fibrinolysins.[11] Crowell[8,9] produced intractable shock in association with hypercoagulable blood by bleeding dogs and maintaining hypotension for prolonged periods. The hypercoagulable state was associated with intravascular clotting and pulmonary emboli. Hardaway and associates[11] demonstrated the development of pulmonary thrombi with associated shock in dogs subjected to the injection of incompatible blood. The pathologic findings in these dogs have a striking resemblance to those in our patient. The appearance of fibrinolysins has been reported after pulmonary operation.[12]

I doubt that the fat embolization contributed much to the clinical picture. The fat may have arisen from the sternum, which was split by the surgical incision. An alternative is suggested by the recent work of LeQuire and associates,[13] who propose that aggregation of blood lipids is responsible for much of the fat seen in fat embolism. It is possible that "plasma emulsifiers" may have been altered concomitantly with alterations in the elements responsible for the coagulation of blood. Although the latter possibility is pure speculation, it seems unlikely that there is a sufficient amount of fat in the sternum

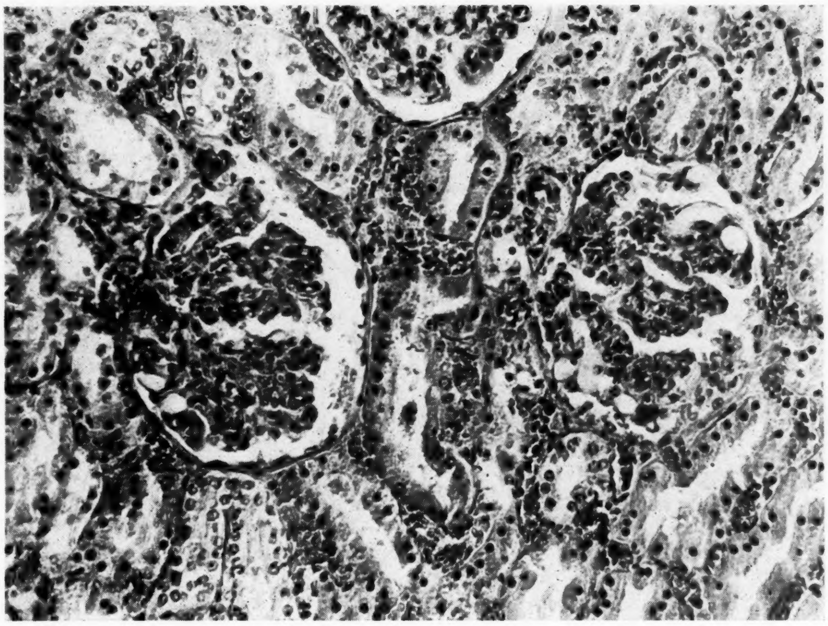

Fig. *10*. Photomicrograph of kidney, showing scattered, dilated, and empty glomerular capillary loops. A fat stain revealed the dilated loops to be filled with fat.

to produce the "emboli" present at the time of autopsy.

DR. REED: *Pathological diagnoses.* (1) Subvalvular aortic stenosis, possibly congenital. (2) Rheumatic myocarditis, mitral stenosis, and aortic stenosis. (3) Multiple widespread pulmonary thrombosis. (4) Fat embolism in kidney and lung. (5) Postoperative status, thoracotomy, aortotomy, and aortic valvulotomy.

## Closing comments

DR. LOVE: It is interesting to speculate what role the active myocarditis could have had in causing the exercise intolerance. We do know that many people carry a very high load of cardiac work for many, many years and have difficulty only when some new event occurs, such as the development of coronary insufficiency or myocarditis.

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# Annotations

## The electrocardiogram in atrial septal defects and atrioventricular cushion defects

The electrocardiogram has proved to be of considerable value in the differentiation of atrial septal defects (ASD) of the ostium secundum type from those of the ostium primum type. Several recent excellent articles attest to this,[1-6] although some observers have failed to confirm this differential diagnostic value of the electrocardiogram.[7,8]

Atrial septal defects of the ostium secundum type may be subdivided into three types: (a) sinus venosus (superior caval); (b) fossa ovalis (central); and (c) inferior caval.[9] It is not possible to distinguish between these subtypes electrocardiographically. Ostium primum defects occur in the lower portion of the atrial septum in the region of the atrioventricular (A-V) valves and are usually associated with a cleft in the anterior leaflet of the mitral valve and occasionally in the septal leaflet of the tricuspid valve. This type has also been called the partial form of persistent common A-V canal.[4,10] In the complete type of persistent common A-V canal, in addition to the ostium primum type of defect in the atrial septum, there is a ventricular septal defect (VSD) and a common A-V valve or fusion of the mitral and tricuspid valves across the top of the ventricular septum with small communications beneath.[4,10] The terms "endocardial cushion defects"[11] or "A-V cushion defects"[4] have also been applied to both partial and complete common A-V canal. Complete absence of the atrial septum is termed "common atrium" or "single auricle."[6,12,13]

The electrocardiogram in ASD of the ostium secundum type characteristically displays an rSR′ in the right precordial leads ($V_1$, $V_{3R}$), and right axis deviation (RAD) in the standard leads. This rSR′ pattern (QRS $<$ 0.12 second) has been found to occur in about 65 per cent of the cases of ASD of the ostium secundum type.[2,3] The pattern of complete right bundle branch block (CRBBB) has been encountered in from 5 to 40 per cent of the cases.[2,3,14] Other patterns which may occur in the right precordial leads include qR, rR′, Rs, rSr′ (normal crista supraventricularis pattern), and rS.[1b,3] The mean QRS axis in most cases lies between +60 and −150 degrees, with the majority lying between +90 and +150 degrees.[1b-3,5,6,15]

The rSR′ pattern (QRS $<$ 0.12 second) in the right precordial leads in ASD has been variously termed "incomplete right bundle branch block,"[5,12-15] "diastolic overload of the right ventricle,"[16] and "right ventricular outflow tract hypertrophy."[3] Cardiac catheterization studies in ASD have demonstrated that there is no delay in the onset of right ventricular systole, such as would occur if there were a true right bundle branch block.[17] Many of the recent studies favor dilatation and/or hypertrophy of the crista supraventricularis region of the right ventricle as the explanation for this pattern.[2,3,17,18]

The rSR′ pattern is usually associated with normal or slightly elevated right ventricular and pulmonary arterial pressures.[1b,3,17] If pulmonary hypertension supervenes and concentric right ventricular hypertrophy develops, the right precordial leads often display a qR or Rs configuration.[1b,3,17,18] The occurrence of a qR or Rs pattern might also suggest the presence of some associated anomaly, such as pulmonic stenosis or even mitral stenosis.[5]

The electrocardiographic pattern which has been found to be nearly pathognomonic of A-V cushion defects is left axis deviation (LAD) in the standard leads with the rSR′ pattern in the right precordial leads. The LAD of the early QRS forces is usually in the range of 0 to −60 degrees,[4,19] whereas the mean QRS axis usually ranges from −60 to ±180 degrees.[1a,6]

Some workers have attributed the LAD to left ventricular enlargement secondary to the mitral insufficiency,[11,20,21] whereas others have favored a parietal wall conduction defect[19] or a congenital aberration of the left bundle branch system.[3-5] Burchell, DuShane and Brandenburg[4] have presented a critical review and rather convincing evidence in favor of the latter explanation.

This distinctive electrocardiographic pattern of LAD has been described in 80 to 100 per cent of A-V cushion defects.[1a,2 3,19] Other workers, however, have not found such a high incidence of LAD, and have even encountered right axis deviation (RAD) in some cases.[7,13] Burchell and associates[4] have encountered some cases of partial or incomplete forms of A-V cushion defects without the typical electrocardiographic pattern, but no cases of the complete form without the characteristic electrocardiogram.

In A-V cushion defects the right precordial leads may also display complete right bundle branch block or qR, Rs, rSr′, or rS patterns which are not diagnostically different from those of ASD of the ostium secundum type. In the presence of mitral insufficiency the left precordial leads may or may not demonstrate left ventricular overloading or hypertrophy. Atrioventricular cushion defects have

been found to manifest q waves in left precordial leads twice as commonly (70 per cent) as do atrial septal defects of the ostium secundum type (35 per cent).[1b,4]

The QRS vector loop in ASD of the ostium secundum type rotates clockwise in the frontal plane and is oriented below the isoelectric line (0 to 180 degrees), to the right and anteriorly.[2-4,22] The QRS vector loop in A-V cushion defects rotates counterclockwise in the frontal plane and is oriented superior to the isoelectric line (0 to 180 degrees), to the left and posteriorly.[2-4,22] A horizontal figure-of-eight pattern oriented along the isoelectric line, with the initial part of the loop rotating counterclockwise, also has been described in A-V cushion defects.[1a,4-6]

The ventricular gradient ($\hat{G}$) in ostium secundum defects tends to be vertical and oriented to the left of the mean QRS ($\hat{A}_{QRS}$), whereas in A-V cushion defects, $\hat{G}$ is horizontal and to the right of $\hat{A}_{QRS}$.[2]

Prolongation of the P-R interval occurs more commonly in A-V cushion defects than in ostium secundum defects.[1b-4] Atrial fibrillation has been described in about 10 per cent of the cases of ASD,[1b,23] being uncommon in the young but more frequent in older persons.[23] Atrial fibrillation is likewise uncommon in A-V cushion defects.[2,3] Tall P waves in Leads II, III, and $aV_F$ are surprisingly infrequent,[2,3,14] although diphasic P waves in Lead $V_1$ ($V_2$) which suggest right atrial enlargement have been described in about 50 per cent of the cases of both ASD and A-V cushion defects.[1a,2]

In patients with common atrium, LAD and counterclockwise rotation of the QRS loop identical to that in A-V cushion defects have been encountered.[5,6] Another interesting feature noted by Keith[5] in cases of common atrium has been a P-wave axis of −60 degrees, together with a short P-R interval.

It is worth emphasizing that ASD of the ostium secundum type may occur with a normal precordial electrocardiogram (without the rSR′ pattern), with a normal axis, and, rarely, with LAD.[1b-3] The frontal vector may also occasionally be oriented superiorly above the isoelectric line or horizontally in a figure-of-eight pattern anu have counterclockwise rotation.[1b,4-6] Of considerable interest has been the observation that ostium secundum defects with acquired mitral insufficiency do not display LAD but may show RAD and clockwise rotation of the frontal vector.[4,5]

Atrioventricular cushion defects occasionally may display a normal QRS axis and rarely even have RAD[3,4] and clockwise rotation of the frontal vector loop.

Patients with pulmonic stenosis, patent ductus arteriosus, ventricular septal defects, or total anomalous venous return present occasionally an electrocardiographic pattern which resembles that characteristically found in ASD of the ostium secundum type.[5,6,21]

Other types of congenital heart disease that may occasionally simulate the electrocardiographic pattern described in A-V cushion defects include: (1) VSD, especially those located posteriorly beneath the septal tricuspid leaflet[4]; (2) combined ostium secundum defect and VSD[5,21]; (3) origin of both the aorta and pulmonary artery from the right ventricle[25]; (4) persistent truncus arteriosus[19]; (5) single ventricle[19]; (6) endocardial fibroelastosis.[19]

Cases of tricuspid atresia display LAD, but the initial forces, although horizontal, are not so leftward as in A-V cushion defects, and the right precordial leads do not exhibit the rSR′ pattern.[19]

In conclusion, it appears that although there are significant exceptions, the electrocardiogram usually will permit a distinction to be made between ostium secundum and A-V cushion defects.

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# Acute angioneurotic edema of the mitral valve

Contemporary literature is barren of references to this particular syndrome. Even Luisada's massive *Cardiology*[1] set has nothing on this topic. Although rare, this condition does exist, and its salient features are worth discussing. Dr. F. Tice diagnosed a case when I was his resident at the Cook County (Chicago, Ill.) Hospital. I have been searching for them since, and in this report, I present my third case.

The young lady in question is now a 23-year-old medical student. She is married and has no children. Since infancy, she has been under constant, careful medical supervision because of various food allergies and asthma. Her family physician thought she had an attack of rheumatic fever when she was 6 years old. He sent her to Arizona, where she spent several years at a boarding school. No doctor ever recorded a cardiac murmur or any other evidence of cardiac pathology.

Since her return to New York, she has been relatively free of symptoms but has continued under close medical observation. In 1958, before entering medical school, she underwent a battery of exhaustive tests. Since everything was considered to be normal, she was permitted to undertake the proposed course. Besides infrequent, trivial upper respiratory infections, the young lady has stayed well. Her last physical check-up was in the summer of 1960.

On Thanksgiving Day of 1960, the patient woke up with a slight cold, but this did not prevent her from preparing the usual Thanksgiving meal. After washing the dishes and cleaning up, she felt tired and so went to bed shortly after 8 P.M. However, the sense of fatigue became progressively worse, and she became very conscious of a pounding, rapid heart beat. At 9 P.M., when I saw her, she was sitting up in bed, badly frightened, and fighting to catch her breath. The pulse was 106, even, and full; oral temperature was 98°F.; the blood pressure was 94/62 mm. Hg; the lungs were still dry and clear, with excellent expansion. The heart presented an amazingly forceful diastolic murmur with presystolic accentuation; also, a maximal systolic murmur was heard; the apical pulsation was marked and a diastolic thrill was felt.

Because of the positive knowledge of the absence of all antecedent cardiac pathology, acute edema of the mitral valve was diagnosed. In the expectation of a rapid subsidence of symptoms, she was reassured maximally, given a sedative hypnotic capsule and an alcoholic beverage drink. She relaxed and fell asleep; I did tell the husband to call me immediately if her symptoms took a turn for the worse. I made clear that radical measures up to emergency cardiac operation could become imperative if closure of the mitral valve threatened.

In the morning the patient was entirely comfort-

able and composed. There was a very marked diminution in the intensity of the murmurs. The ECG showed only some P-wave inversions. The complete blood count was normal except for a 5 per cent eosinophilia. No further medication was deemed necessary, although bed rest was enforced. After another day, all physical abnormalities were gone; the heart sounds had reverted to complete normality. The following week, the student health center conducted searching tests, including barium swallow in the oblique positions, fluoroscopy, blood tests, ECG, etc. Everything checked out entirely normal.

Three months later her husband developed a very severe upper respiratory infection. Two days later the patient called me to say that she was beginning to feel again as she had on the previous occasion. Although this attack was not nearly so intense as the first one, the double murmur in the mitral area was clearly audible again. This time the patient received a 4-mg. tablet of Chlor-Trimeton in addition to the sedation. Within 2 hours the murmurs were gone completely; no epinephrine was needed. She has been well since.

*Comment.* Obviously, histologic sections would be needed to actually *prove* the presence of the acute edema. However, the rapid fluctuation in the signs is quite characteristic. It is easy to exclude such entities as ball thrombus on either side of the heart.[2,3] Tumors of the endocardium behave in their own definite way.[4] There is no infection that can give this rapid alternation of signs. Acute allergic Fiedler's myocarditis can come on with startling rapidity but has its own, quite different, course.[5] The treatment with antihistaminics, sedation, and rest has been quite adequate in the three cases within my experience. Use of epinephrine and oral ephedrine would be logical.

A fairly careful search of the literature reveals a single reference[6] to a "mitral valvulotomy for an edematous mitral stricture." In this instance, the French surgeons had a 33-year-old woman who had had chorea at the age of 13. Her ordinary clinical picture was that of a mild mitral insufficiency. Yet, she was subject to repeated crises of paroxysmal tachycardia, pulmonary edema, nocturnal hemoptysis, and even periods of unconsciousness. The attending physicians concluded that the mild mitral stenosis was being aggravated by periodic bouts of edematous swelling of the valve, which would then become shut tight almost completely. On April 7, 1951, the surgeon did a finger fracture of the stenotic valve. "Du souffle systolique disparition" was paralleled by an excellent clinical recovery.

Ordman[7] deals with "urticaria" in considerable detail but does not mention cardiac valvular disease. An exhaustive article by Trigg[8] entitled "Hereditary Angioneurotic Edema" has 34 references, but again, nothing is said about the mitral valve. Pathologists do not seem to have described this entity even though logic would seem to require that some instances of acute edema of the cardiac valves as described above must end lethally. Is it possible that the condition goes unrecognized on the autopsy table?

It is hoped that the present clinical note may again draw attention to the fact that epinephrine can possibly be lifesaving when given in time. Also, at times, emergency cardiac operation could be of tremendous value—again, when done in time. Acute edema of the mitral valve will begin to be diagnosed again when this syndrome is recalled from limbo to general recognition.

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# Pulmonary artery dilatation as a cause of chest pain

The article by R.S. Ross[1] on "Right Ventricular Hypertension as a Cause of Precordial Pain," published in the January, 1961, issue of the *American Heart Journal*, provides further evidence that the chest pain in pulmonary stenosis and pulmonary hypertension is the result of right ventricular myocardial ischemia secondary to reduced coronary blood flow, which is explained on the basis of elevated right ventricular intracavitary pressures during both systole and diastole.

In 1953, we reported chest pain in 3 cases of congenital heart disease with dilatation of the pulmonary artery.[2] The diagnoses in these cases were: (1) pulmonary stenosis with atrial septal

defect, (2) atrial septal defect, and (3) idiopathic pulmonary artery dilatation. It was then already stressed that chest pain may occur without pulmonary hypertension. It was also pointed out that the disproportion between coronary blood flow and right ventricular work may explain the chest pain only in the patient with pulmonary stenosis. It may, however, be a contributing factor in the second patient with atrial septal defect and diastolic overload of the right ventricle. But this mechanism can certainly not be held responsible for the chest pain observed in the patient with idiopathic pulmonary artery dilatation, in whom right ventricular and pulmonary arterial pressures were shown to be completely normal. Since then we have observed 6 additional patients with idiopathic pulmonary artery dilatation; all cases were proved by cardiac catheterization. The right ventricular systolic and diastolic pressures, as well as the pulmonary arterial pressures, were normal, and there were no significant changes in the oxygen content of the blood in the right side of the heart. In 5 of these patients, chest pain was a prominent feature. The pain was sometimes brought about by physical exertion, but also occurred at rest. The pain lasted from a few minutes to several hours. It was frequently associated with dyspnea, but was not relieved by nitroglycerin. The exercise test (Master) was negative.

Since the common denominator in the cases which we previously reported[2] and in the other 5 patients with idiopathic dilatation of the pulmonary artery is dilatation of the pulmonary artery, the possibility has to be considered that the chest pain may be elicited by distention of the walls of the pulmonary artery even when pulmonary arterial pressure and right ventricular pressure are not elevated. Possible afferent pathways from the pulmonary artery are indicated by Viar and Harrison.[3]

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# A letter from Sir James Mackenzie to Sir Thomas Lewis*

An intimate account of the life of Sir James Mackenzie has been given by his friend and pupil, R. McNair Wilson, in his book so aptly titled, *The Beloved Physician*. The letter here reproduced, presented by Sir Thomas Lewis to the late Dr. William P. St. Lawrence, a Fellow of the Academy (New York Academy of Medicine), refers briefly to several matters with which the name of the writer is closely associated. It also reflects the informality of the relationship which existed between two men who have exerted a profound influence on the direction of thought in the field of cardiology.

It was Mackenzie who first described atrial fibrillation in his book, *The Study of the Pulse*, in 1902. At this time he referred to it as "paralysis of the auricles." Only some years later, after devising the ink polygraph and analyzing tracings from patients, did he recognize the true nature of the condition. The subsequent studies of Lewis, made with the aid of the electrocardiograph, defined and clarified the mechanism of fibrillation.

Mackenzie always insisted on the importance of symptoms and of accurate bedside observation. To carry out his ideas, in 1918, at the age of 65, he gave up his Harley Street practice and moved to St. Andrews in Scotland, there to establish, one year later, The Institute for Clinical Research, which now bears his name. Not long after he had made this move, anginal pains, first noted some years previously, became more pronounced, and he died of acute myocardial infarction at the age of 72. In the meantime, in 1923, he had published his classical volume, *Angina Pectoris*.

In the book, *The Future of Medicine*, referred to in the letter, Mackenzie expounded his views on this and other related subjects. There were numerous critics of his doctrine; yet, these, like his many friends, loved and admired him. To the end, he belittled the use of "mechanical devices" and continued to stress the fundamental importance of clinical research. Late in life, he once remarked to Wilson, with a smile: "If I had never invented the ink polygraph, I might never have obtained a hearing at all."

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*Presented to the Library of the New York Academy of Medicine by Mrs. William P. St. Lawrence. Reprinted, by permission of the New York Academy of Medicine, from the *Academy Bookman*, Vol. 14, No. 1, p. 6, 1961.

New Park St. Andrews
Dec 4/18

"Dear Lewis,

"I suppose you agree that the course I approve in nearly every instance is a stimulation of the respiratory centre, & the chief source of stimulation is a deficient blood supply. The nature of the actual stimulant, deficient O, excessive $CO_2$ in lactic or other acid. This latter problem I do not attempt to deal with as all the conflicting theories & experiments are beyond my comprehension.

"In your argument if I understand you aright, you say if there is no cyanosis therefore the breathlessness is not cardiac in origin, I see we are at cross purposes. If a man with complete heart block goes rapidly up a hill he becomes breathless. My explanation is that the heart does not increase its output, as its rate is uninfluenced. The demand for an excess supply to the muscles of the leg diminishes the amount to the respiratory centre & so causes breathlessness —without cyanosis. Rarely such patients in place of being breathless are uncertain feel as if they would fall or the feet feel very heavy—signs I take it of deficient supply of blood to brain & legs. Many cases of auri-fibrillation are cyanotic & very breathless, some are breathless & not cyanotic. Even in cases of Cheyne-Stokes due to auri-fibrillation there is little cyanosis (I think sometimes none) but on digitalis slowing the rate the Cheyne-Stokes disappear.

"Henry James for a year or 2 was pulled up every 200 yards by pain, then he developed auri-fibrillation & was pulled up every 100 yards by breathlessness, & no cyanosis.

"I heard from Christian that he had written you for an article on mechanical aids in diagnosis of circulatory troubles. It tickled me for in my article I intend to demonstrate that the use of mechanical devices in the routine observation in practice is indicative of a lack of skill in the physician & evidence that he has not passed out of the Chrysalis stage! I have just finished once over the book I have been engaged on—The Future of Medicine—& I hope it will cause some searching of hearts, & I deal very faithfully with laboratory methods.

"I paid a visit to MacWilliam a few days ago & he has some very pretty stuff on fibrillation. Matthew Hay dined with us, & he is one of the Carnegie trustees with 2¾ millions at their disposal. He told me if I liked I could have any amount of money for my new research institute. I told him I was afraid it might prove a failure, & I would rather not have the disgrace of getting money & not show a useful result. He was good enough to say that they would not hesitate in giving the money to me even with such a prospect. And here have I made myself a bond slave to an American publisher quite unnecessarily, particularly as the research will not be a failure. Already it is panning out far better than I dared expect, & once we get the thing going I am now confident that the lines I intend to follow will be fruitful. At present I can't get the apparatus nor the assistants, although I have partially engaged 2 or 3. My hands too are rather full with the Future of Medicine, & I have next to write a treatise for the confounded American. After that I hope to have the assistants & go full steam ahead.

"We thoroughly enjoy this place & the days flee past. I would strongly advise you to (put) down tools every now & again & flee away & laze about & "think," real downright hard thinking. It is surprising how different my problems look since I came here, & I feel like the eagle when youth was renewed. The local guidebook tells of decrepit men of 70 coming here to die, & they buck up & lead enjoyable lives till they get to 90. And here am I beginning a new sport —curling—& shouting like a school boy.

"With best regards to Mrs. Lewis

Believe me yrs. ver. t.
J. Mackenzie"

# Book reviews

ARTERIOSKLEROSE: ÄTIOLOGIE, PATHOLOGIE, KLINIK, UND THERAPIE. Edited by Prof. Dr. Gotthard Schettler, Direktor der Medizinischen Klinik Stuttgart-Bad Cannstatt, Apl. Professor an der Universität Tübingen. In collaboration with Prof. Dr. H. Bredt, Mainz, Wiss. Rat Dr. H. Harlfinger, Tübingen, Priv.-Doz. Dr. J. Lindner, Hamburg, Prof. Dr. Ch. Rob, London, Prof. Dr. H. Sautter, Hamburg, and Prof. Dr. W. Schulte, Tübingen. Stuttgart, 1961, Georg Thieme Verlag, 728 pages. Distributed in the U.S.A. and Canada by International Medical Book Corp., New York. Price $24.50.

In our "Golden Age" of curative medicine and increasing longevity, the problem of arteriosclerosis has assumed overwhelming significance. Although the sheer quantity and the ingenuity of the investigative work devoted to it measure up well to its size, we are still facing a painful disproportion between magnitude of effort and conclusiveness of results. Under such frustrating conditions it was a heroic undertaking of the author, himself an experienced investigator, to present the entire problem complex of arteriosclerosis in one large volume, assisted by six competent co-workers who contributed some specialized chapters.

The first half of the book deals with the basic questions of morphology, chemistry, etiological factors and their statistical evaluation, and covers such subjects as "static" and "dynamic" angiochemistry, the role of sex, heredity, hormones, infections, allergy, psychosomatic stress, hemodynamics, nicotine, toxic substances, blood coagulability, and diet. This multifaceted material is treated in a soberly critical fashion and has extensive references to the American literature. The diagnostic limitations of lipoprotein and serum cholesterol values are pointed out. The established importance of dietary fat intake and of the balance between saturated and unsaturated acids is recognized, but not without a warning against arbitrary and uncritical dietary fads.

It is fascinating to compare the contents of Schettler's book with earlier reviews on arteriosclerosis, e.g., Cowdry's volume which was published in 1933, and to notice the shift in emphasis from morphology to histochemistry, and from individual observations to epidemiological statistics.

The second, clinical half of the book gives a vivid picture of the progress which has been made in diagnostic procedures and of the spectacular advances in vascular surgery. Clinical manifestations of arteriosclerosis in all sections of the vascular tree are discussed in detail, illustrated by interesting case histories, and complemented by special chapters on psychiatric and medicolegal aspects. Physiotherapy, the use of hormones and of drugs which influence lipid metabolism, and carefully prepared dietary tables for the German household occupy the concluding chapters.

Having in mind the regretable, but inevitable, separation of interests of most basic investigators, on the one hand, and of clinical research workers and practicing physicians, on the other, this reviewer wonders whether the book will prove equally useful to all of its readers. However this may be, the fact remains that we have here a monumental achievement of unquestionable value as a guide to serious students of the problem of arteriosclerosis in its many manifestations. The style is fluent and less ponderous and involved than much of the German scientific postwar writing. The illustrations are beautiful, if not lavish. Altogether, Schettler's book is unparalleled in present-day literature on the subject of arteriosclerosis.

In order not to neglect his obligation of flawfinding, this reviewer would like to mention from his own point of view that, in the discussion of coronary heart disease and angina pectoris, more clarity in the differentiation between the essentially vascular and the essentially myocardial phenomena involved might have been desirable.

This book can be heartily recommended to all those who are interested in or who should be interested in arteriosclerosis.

VARICOSE VEINS. A PRACTICAL MANUAL. By R. Rowden Foote, London. With the assistance of A. Gordon Dingley, M.A., M.Chir. (Cantab.), F.R.C.S., Consultant Surgeon to the Southend-on-Sea Group of Hospitals; Late Surgical Chief Assistant, St. Bartholomew's Hospital, London. Third edition, Bristol, 1960, John Wright and Sons, Ltd. Exclusive U.S. agents, Williams & Wilkins Co., Baltimore, Md., 356 pages. Price $13.

This book on varicose veins is now in its third edition, which attests to its wide acceptance. It deals comprehensively with all aspects of varicose veins and related problems. The book is written in an informal, readable style. It is exceptionally well illustrated and thoroughly annotated. The author has accomplished his purpose of providing a "Practical Manual" on the management of varicose veins, and the book is highly recommended to physicians and surgeons who deal with these problems.

ESSENTIAL HYPERTENSION. An International Symposium, Berne, June 7-10, 1960, sponsored by CIBA, under the chairmanship of F. C. Reubi. Edited by K. D. Bock and P. T. Cottier. Berlin, 1960, Springer Verlag, 392 pages, 81 illustrations. Price: DM 33.80. Published in an English edition also.

This international symposium concerned with essential hypertension has been carried on in the fine tradition of other CIBA symposia and constitutes an authoritative review of the subject by a distinguished international group of investigators. The subject is very well covered in broad outlines. The book constitutes a good general review of the field of essential hypertension and

includes a discussion of etiology and, especially, therapy. Pathology of the disease is discussed only incidentally.

The informed reader will find very little that is new in this volume. He will find, however, a discussion of most of the important developments during the last 10 to 20 years, with references to a large amount of investigation during this period of time. Much controversial material is presented, and, in this light, the free, sincere discussions are particularly valuable since many opinions are expressed.

The book is recommended as a general outline of accomplishments in the field of research and therapy of essential hypertension in recent years and as a source of literature from which additional reading may be done.

HYPOKINETIC DISEASE. By Hans Kraus, M.D., Associate Professor of Physical Medicine and Rehabilitation, New York University, New York; and Wilhelm Raab, M.D., F.A.C.P., F.A.C.C., F.C.C.P., F.A.C.S.M., Active Emeritus Professor of Experimental Medicine, and Director of the Cardiovascular Research Unit, University of Vermont College of Medicine, and Attending Physician, DeGoesbriand Memorial Hospital, Burlington, Vt. With a foreword by Dr. Paul D. White. Springfield, Ill., 1961, Charles C Thomas, Publisher, 193 pages. Price $7.50.

This is an interesting and challenging book. Its major thesis is the harmful effects of the modern sedentary life, particularly in the United States. The first portion deals with orthopedic disorders and especially with the value of physical exercise as a method of treatment.

The second part of the book is concerned with cardiovascular disorders and includes a comprehensive and scholarly review of the physiologic, clinical, and statistical literature. The last portion concerns the relationship between lack of physical conditioning and emotional instability.

Numerous charts and diagrams, some of them of humorous nature, as well as tables, clarify the text.

The authors emphasize that the so-called athlete's heart is abnormal only in the sense that it is supernormal. Actually, they consider the athlete's heart to be the normal heart, and the heart of a sedentary individual to be functionally abnormal. They emphasize repeatedly that these are not fixed differences, but may be altered in either direction by prolonged rest or by periods of training.

A reviewer who wished to emphasize the picayunish qualities which seem to be innate in many reviewers can find a number of minor flaws. For instance, one questions the data quoted on page 68 which indicate an average cardiac output of 2.1 liters per minute for the trained individual as compared with 5.5 liters for the untrained. Similarly, there is, perhaps, an excessive emphasis on the role of adrenergic substances in the etiology and pathogenesis of the difference between the hearts of untrained and trained subjects. Many readers will regard this emphasis as interesting, but based on theoretical rather than proved concepts.

These are minor defects. Actually, the evidence assembled from a wide variety of sources and clearly presented is almost overwhelming in indicating the importance of physical exercise as a means of achieving positive health in the normal population and as a means of reducing the likelihood of coronary and other degenerative diseases in the older age groups.

The extensive bibliography alone would make the book worth while for the laboratory or clinical investigator as well as for the practicing physician. The various hypotheses advanced by the authors are supported by a considerable body of evidence and are both challenging and stimulating.

FLOW PROPERTIES OF BLOOD AND OTHER BIOLOGICAL SYSTEMS. Edited by A. L. Copley and G. Stainsby. Proceedings of an informal discussion convened jointly by the Faraday Society (Colloid and Biophysics Committee) and the British Society of Rheology, held at the University Laboratory of Physiology, Oxford, Sept. 23 and 24, 1959. New York, 1960, Pergamon Press, 446 pages. Price $12.50.

A joint meeting under the sponsorship of the British Society of Rheology and a committee of the Faraday Society was held in Oxford, England, September, 1959, to discuss aspects of the current status of "Biorheology," i.e., the study of flow and deformation in biologic materials. This volume contains the contributions presented by 48 authors, as well as the informal discussion of each of these papers. These are grouped into five sections: (1) a general lecture on the rheological properties of concentrated polymer solutions; (2) eleven papers dealing with "Heamorheology"; (3) ten papers relating to systems other than blood; (4) short discussions of ten exhibits of specialized apparatus; and (5) brief descriptions related to seven scientific films.

This book follows the recent trend of publishers to give impressive and somewhat misleading titles to reports of specialized conferences of this type. This work is not necessarily a systematic description of the present status of knowledge of the flow properties of blood; however, it does provide an introduction to major areas of activity in this field. The participants in this conference included physiologists, hematologists, physicians, surgeons, physicists, chemists, mathematicians, and engineers. The papers are highly technical and deal with the rheological properties of substances ranging from hot chocolate and dead fish to cervical mucus, lymph, and blood. This report will be useful to those who wish to make a quick survey of activity in this expanding field of investigation. It will be of very limited interest to the great majority of clinical cardiologists, or to those investigators whose major interest does not touch on this area.

# Announcements

The American College of Cardiology's deadline for the Young Investigators Award for 1962 is January 1, 1962, according to an announcement by Gabriel F. Greco, M.D., Ozone Park, N.Y., Chairman, Public Relations Committee.

This award is represented by a silver medal and $1,000. There will be one honorable mention award and $250, and eight additional awards of $100 each.

Any physician in residence or fellowship status, or within 3 years following this residence or fellowship, is eligible to participate with a formal presentation, 10 minutes in length, describing original investigation, placed in competition, before the Eleventh Annual Meeting of the American College of Cardiology in Denver, Colo., May 29 to June 2, 1962. An original manuscript and letter indicating intention to enter competition must be accompanied by a letter from the chief of the service or laboratory indicating his willingness to have the material placed in the competition.

Address queries and manuscript to: Executive Director, American College of Cardiology, Empire State Bldg., 350 Fifth Ave., New York 1, N.Y.

Reprints are available for the Conference on Mechanisms of Experimental Renal Hypertension, held in Augusta, Mich., April 22 and 23, 1961, with Dr. S. W. Hoobler, Ann Arbor, Mich., as Chairman, and Dr. A. C. Corcoran, Cleveland, Ohio, as Vice Chairman.

The program was as follows: *Review of Physiologic Mechanisms:* Renin—Dr. P. Blaquier, Ann Arbor, Mich.; Liver—Dr. H. F. Loyke, Cleveland, Ohio; Adrenal—Dr. P. Rondell, Ann Arbor, Mich.; Kidney—C. Wilson, London, England. *Review of Vessel Wall Changes:* Reactivity of Arterioles—Dr. D. F. Bohr, Ann Arbor, Mich.; Arteriolar Rigidity—Dr. J. Conway, Ann Arbor, Mich.; Effect of Hypertension on Vessel Walls—Dr. G. Masson, Cleveland, Ohio. *Review of Humoral Substances:* Anti-Hypertensive Substance From Kidney—Dr. E. Muirhead, Detroit, Mich.; Anephrotensin—Dr. R. Rosas, Santiago, Chile; Angiotensin—Dr. Skeggs, Cleveland, Ohio, and Dr. Boucher, Montreal, Canada; Renin—Dr. Helmer, Indianapolis, Ind.

Abstracts of discussion by the following additional participants: Dr. L. Beck, Dr. R. Correa, Mr. John Schroeder, Mr. R. Warzynski, all of Ann Arbor, Mich., Dr. F. Bumpus and Dr. E. Haas, of Cleveland, Ohio, Dr. W. Freyburger, Kalamazoo, Mich., and Dr. J. Genest, Montreal, Canada.

The reprint, containing about 50 pages of original work and reviews, may be obtained free of charge by written request to: Dr. Walter Freyburger, Upjohn Company, Kalamazoo, Mich.

The University of Texas Postgraduate School of Medicine is pleased to announce a Symposium on Cardiac Arrhythmias scheduled for Dec. 8, 9, and 10, 1961. The symposium will be held in the Texas Medical Center, Houston, Texas, and the program will be presented by three outstanding guest lecturers, augmented by a local faculty. The three guest lecturers are: Dr. Samuel Bellet, of Philadelphia, Dr. David Scherf, of New York City, and Dr. Paul Zoll, of Boston.

For further information, write: Office of the Dean, The University of Texas Postgraduate School of Medicine, 102 Jesse Jones Library Building, Texas Medical Center, Houston 25, Texas.

The American College of Cardiology will hold a Workshop in Cardiology at the Institute for Cardiopulmonary Diseases of the Scripps Clinic and Research Foundation in La Jolla, Calif., Dec. 5-8, 1961, according to an announcement by Gabriel F. Greco, M.D., Chairman, Public Relations Committee. E. Grey Dimond, M.D., President of the College, will preside, assisted by 24 instructors from the Institute.

Coverage of recent developments in basic and clinic research will include: principles and diagnostic value of electrocardiography, vectorcardiography, phonocardiography, cineangiography, indicator-dilution studies, monitoring of cardiovascular events, respiratory instrumentation in congenital and acquired heart disease; the biochemistry of myocardium and blood vessels, with emphasis on relationships of the carbohydrates, the cardiac glycosides, the lipids, and the catecholamines to clotting mechanisms in disease. There will be case presentations, clinical pathologic sessions, question and answer periods, panel discussions, illustrated by a profuse number of tracings, x-rays and laboratory findings.

The program will run four full days, from 9:00 A.M. to 5:00 P.M. daily, and two evening sessions from 7:00 P.M. to 9:00 P.M. Tuition is $50.00 for members and fellows of the American College of Cardiology, and $100.00 for other physicians. Residents and internes will be admitted without charge. Advance enrollment is required.

For further information, write: Philip Reichert, M.D., Executive Director, American College of Cardiology, Empire State Bldg., New York 1, N.Y.